Process Management Applications in Biopharmaceutical Drug Production

by

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Submitted to the MIT Sloan School of Management and the Engineering Systems Division in Partial Fulfillment of the Requirements for the Degrees of

Master of Business Administration
and
Master of Science in Engineering Systems

In conjunction with the Leaders for Global Operations Program at the Massachusetts Institute of Technology

June 2011

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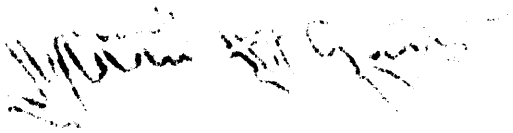

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Abstract

Genzyme's manufacturing and supply chain organization is responsible for the production and delivery of medically necessary medicines for patients with rare diseases around the world. Because of the nature of the products produced at Genzyme, a lapse in operational performance has societal as well as economic impacts. Therefore increased understanding of the complex production systems at Genzyme is helpful to reduce risk and improve performance.

This thesis is an analysis of a system of two critical production processes at Genzyme. These processes are studied collectively because shared resources make them a tightly coupled system. The research is presented in three sections. The first section explores the current state of the system and explains general performance trends. The second section examines the impact of scheduling complexity arising from shared resources. The third section discusses how process improvement methodologies could be applied at Genzyme.

The following conclusions arise from the work conducted for this thesis. First, the performance of the system has declined due to an increase in utilization and an already high level of variability. Second, variability caused by shared resource conflicts can be minimized using new scheduling techniques. And finally, continuous improvement methods are recommended to further reduce variability and increase overall process performance.

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Acknowledgments

I would like to thank the Leaders for Global Operations (LGO) program at MIT, my classmates in the 2011 class of LGO, and the many faculty members that helped guide my learning over the past two years – especially my thesis advisors.

I also appreciate the support and help provided by Jordan Bedford, Adam Kulczyk, Paula O'Donnell, and the many other Genzyme employees who supported my work, took chances on my suggestions, and gave me a hands-on learning experience in biotech.

Finally, and most importantly, I am eternally grateful to my family. This work and my participation in the LGO program would not have been possible without the support and sacrifice of my wife Kerin. My son Sean, born during my time in LGO, has already enriched my life in countless ways.

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Note on Proprietary Information

The information in this thesis has been masked to protect the intellectual property of the Genzyme Corporation. Specific details such as production site location and identifying production process details have been intentionally omitted. Process performance data has been masked to hide actual values.

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1 Introduction

1.1 Project Context

Genzyme is one of the world's leading biotech companies specializing in the discovery and development of treatments for rare diseases. After many years of significant growth, Genzyme experienced production related problems at its Allston, MA production facility. A viral contamination in 2009 interrupted production of key products resulting in depleted inventory and eventual product shortages.

Given the critical nature of biopharmaceutical products, supply chain issues can cause significant problems for patients. In this particular industry stock-outs can literally mean life or death. This reality requires Genzyme and other similar firms to understand and monitor the performance of their production processes in great detail. It is important to identify and remove weaknesses in anticipation of potential environmental shocks to the system.

This thesis presents a three part analysis that proposes a method to assess, monitor, and improve critical processes in biopharmaceutical supply chains. The first analysis is a study of two closely related production processes at Genzyme that identifies the causes of a decrease in performance over time. The second explores a potential solution to some of the problems uncovered in the first analysis. The third study proposes a general framework to monitor and improve both the processes considered in the first two analyses and can be applied to other critical areas of the supply chain.

1.2 Thesis Overview

This document is organized as follows:

Chapter 1 provides general background relevant to this project as well as a summary outline of the document.

Chapter 2 starts with a summary description of Genzyme history with a focus on recent operational performance. The chapter continues to introduce a system of two critical production processes at a Genzyme facility. A process management framework used to analyze the Genzyme processes is introduced including relevant literature review. The framework relates process variability to capacity utilization and buffers such as time and inventory. Chapter 2 concludes that performance of the production processes has declined due to an increase in utilization concurrent with a high level of variability and a fixed amount of inventory.

Chapter 3 is the second analysis in the document. It reviews the findings from the first analysis and proposes a method to improve the performance of the system; namely, reducing variability and capacity utilization through fixed, resource-based scheduling. Historical data is used to simulate the effects of implementing the schedule and comparing hypothetical process performance to actual results. The simulation demonstrates an improvement through the use of a fixed schedule; however this solution alone does not provide an optimum.

Chapter 4 is the final analysis of this thesis. Building on findings from the first two studies, this chapter proposes a framework of continuing analysis and improvement. A summary review of process improvement literature provides background for specific implementation at Genzyme. Example monitoring and problem solving tools are described for the processes studied throughout this thesis. The conclusion includes a recommendation for implementing the techniques across other Genzyme processes.

2 Analysis 1 – Process Overview

2.1 Background

2.1.1 Genzyme

Genzyme is one of the world's leading biotechnology companies. The corporation focuses on developing and applying life science technologies to help patients with rare inherited disorders, kidney disease, cancer, transplant, and immune disease[1]. Founded in 1981, Genzyme began clinical trials for its first major product, Ceredase®, in 1984. Ceredase treats patients with Gaucher Disease and was designated an orphan drug in 1986 by the United States Food and Drug Administration (FDA). Orphan drugs treat rare diseases affecting fewer than 200,000 people[2] and are awarded special regulatory protection beyond typical medicines.

In 1996 the FDA granted marketing approval for Cerezyme®, a replacement for Ceredase, to be produced at a state-of-the-art facility in Allston, Massachusetts. Cerezyme is still Genzyme's highest selling product by revenue. Throughout the 1990s and 2000s Genzyme continued to grow and expand eventually owning and operating production facilities in the United States and Europe and expanding its portfolio to include 20 products worldwide[3].

Genzyme's 2009 revenue was $4.5 Billion with 39% of that total derived from sales of products that target rare genetic diseases[4]. Global headcount eclipsed 10,000 employees.

2.1.1.1 Biotech Drug Production Process

Most biotech companies, including Genzyme, produce their products by altering the DNA of a mammalian cell to produce a product suitable for humans. Genzyme protein therapeutic medicines are created by manipulating cells and then replicating them in large numbers using processing tanks called

[1] (Genzyme Corporation, 2002-2011)
[2] (Genzyme Corporation, 2011)
[3] (Genzyme, 2010)
[4] (Genzyme, 2010)

bioreactors. Inside the bioreactors the cells produce enzymes which are harvested and later purified and formulated into doses suitable for injection into humans.

2.1.1.2 Recent Events

Recent events at Genzyme provide an important setting for the project undertaken with this thesis. After years of successful execution, Genzyme dealt with a number of recent operational setbacks. A string of production related problems including quality, regulatory compliance, and product supply issues slowed Genzyme's growth and forced the company to reevaluate its operations. Production was impacted at the Allston plant which, at the time, produced Cerezyme, Fabrazyme, and Myozyme, drugs that treat genetic disorders, and filled Thyrogen, a treatment for thyroid cancer complications. The following sections summarize key events during this time period.

2.1.1.2.1 FDA Inspection Findings

In fall of 2008 the Food and Drug Administration conducted an inspection of Genzyme's Allston Landing Facility located in Boston, Massachusetts. Following the visit, the FDA sent Genzyme an inspection summary letter cataloging a number of deficiencies in the manufacturing process at Allston including a lack of procedures for preventative maintenance, improper documentation practices, and failure to validate equipment and processes[5].

2.1.1.2.2 Viral Contamination

In June of 2009 a virus was discovered in a vessel used to produce Cerezyme at the Allston plant. The virus attacked the cells used to produce the enzymes that are formulated into Genzyme medicines. The virus was later determined to be a strain called vesivirus 2117 which is not harmful to humans but hinders the drug production process. Once the virus was discovered, all production at the Allston plant was stopped to focus on resolving the problem[6].

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[5] (United States Food and Drug Administration, 2008)
[6] (Armstrong, 2009)

2.1.1.2.3 Production Stoppage

The Allston facility stopped producing for more than six weeks starting in June of 2009. Remediation efforts included the disassembly, sanitization, and in some cases replacement of equipment throughout the plant. The Allston plant came back online in late July of 2009. During the plant stoppage inventories of both Fabrazyme and Cerezyme were depleted, causing shortages.

2.1.1.2.4 Consent Decree

The FDA returned to the Allston facility for an inspection in October/November of 2009. Their findings and reports identified deficiencies in the quality assurance, training, documentation and other practices at the site[7]. In March 2010, the FDA informed Genzyme that they intended to take further enforcement action which led to the consent decree entered in the courts in April 2010. In order to continue producing products at Allston, Genzyme and the FDA agreed to terms including a $175 million fine, the removal of the fill / finish operations from the plant, and a multi-year commitment to have a third party compliance consultant oversee all activities at the site[8].

2.1.1.2.5 Financial / Patient Impact

The production interruption at Allston caused supply problems including the rationing of Cerezyme and Fabrazyme to the most critically afflicted patients around the world. Immediately following the Allston production stoppage Genzyme executives expected the supply shortages for Cerezyme and Fabrazyme to last 6-8 weeks[9] but have adjusted their estimates multiple times. As of January 2011 Cerezyme is being delivered to patients with no restrictions,[10] Fabrazyme is expected to return to normal levels the second half of 2011.[11]

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[7] (United States Food and Drug Administration, 2009)
[8] (United States Food and Drug Administration, 2010)
[9] (Genzyme Corporation, 2009)
[10] (Genzyme Corporation, 2011)
[11] (Genzyme Corporation, 2011)

The product shortages have impacted both patients and Genzyme's business. Prior to the contamination Cerezyme was the only product available to treat Gaucher disease. Due to the crippling and life threatening nature of these diseases the FDA gave fast track approval to drugs developed by Shire and Protalix BioTherapeutics to help patients who had been taking Cerezyme[12].

The combination of manufacturing interruption, FDA pressure, and new competition caused Genzyme's stock price and market value to decline starting in mid-2008. Genzyme was trading at over $80 per share in early 2008 but fell to under $50 per share as the supply chain problems persisted into the spring of 2010.

2.1.1.2.6 Activist Investor Interest

As Genzyme's stock price fell activist investors became interested in the company. Most notably Carl Icahn purchased over 10 million shares and attempted to remove CEO Henri Termeer through a proxy battle. Prior to his moves with Genzyme Icahn used proxy battles to get seats on the board of another biotech firm, Biogen Idec, and pushed company leaders to sell or split up the company.[13]

2.1.1.2.7 Sanofi-Aventis Merger

In the summer of 2010 French pharmaceutical giant Sanofi-Aventis made a public bid to acquire Genzyme.[14] While Genzyme initially did not agree on the offer price[15], at the time of this writing Sanofi-Aventis has closed the deal and now owns a controlling stake in Genzyme[16].

2.1.1.3 Project Implications

This period of operational trouble impacting patients and ultimately causing financial distress for Genzyme sets the background for the importance of the research presented in this thesis. While the viral contamination could be considered an unfortunate and unlikely event, restoring inventory levels for

[12] (Reuters News, 2010)
[13] (Dow Jones Business News, 2010)
[14] (Cimiluca & Whalen, 2010)
[15] (Nicholson, 2010)
[16] (Serafino, 2011)

Cerezyme and Fabrazyme has presented many operational challenges. Any organization that produces a product or provides a service must understand all the complexities, interactions, and risks of their operations in the interest of meeting the needs of the business. This is especially true when producing medically necessary products.

This backdrop of recent events at Genzyme underscores the importance of the work presented in the remainder of this thesis. The focus of the following analysis is two production processes at a single Genzyme manufacturing facility. The objective of the research is to improve understanding of the drivers of process performance, identify opportunities for improvement, and provide a framework to apply these methods to other processes at Genzyme. The next section of the document introduces the production processes and describes their place in the Genzyme supply chain.

2.1.2 Project Scope

2.1.2.1 Process Introduction

The focus of this research project is two processes executed at a Genzyme production facility. Each process consists of the interaction of people, equipment, and information necessary to complete a part of the production process for a particular product. For the remainder of this document the word "process" will refer to the general concept of all of the resources and tasks associated with a particular procedure. We study two processes because they share resources such as auxiliary equipment, and operations staff, and these dependencies create complex interactions that require both be examined together as a system. The processes are not new to Genzyme. In both cases, they have been carried out in the particular facility in question for a number of years. What makes them relevant and interesting is the heightened awareness around process performance given recent events at Allston.

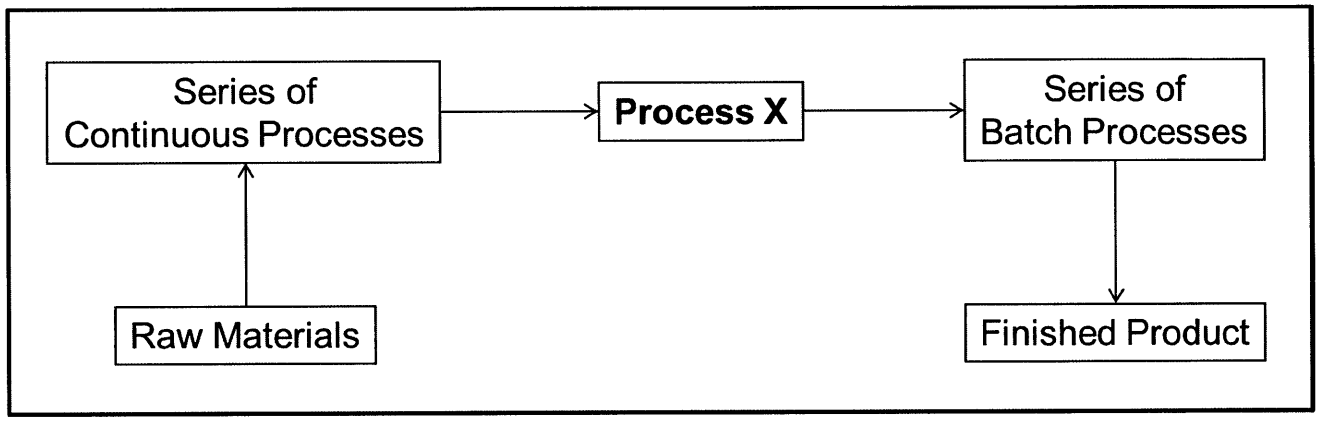
To protect proprietary Genzyme information product and process specific information is masked. As each process is unique we will use the designation "X" and "Y" for the remainder of this document.

For example process X supports the production of product X and process Y supports the production of product Y.

2.1.2.1.1 Process X

Process X is an intermediary step in the production of product X shown in Figure 1. It is the point in the production of product X where the process goes from primarily a continuous process to primarily a batch process. Process X consists of a continuous transportation step, a holding step, and a value added batch step.

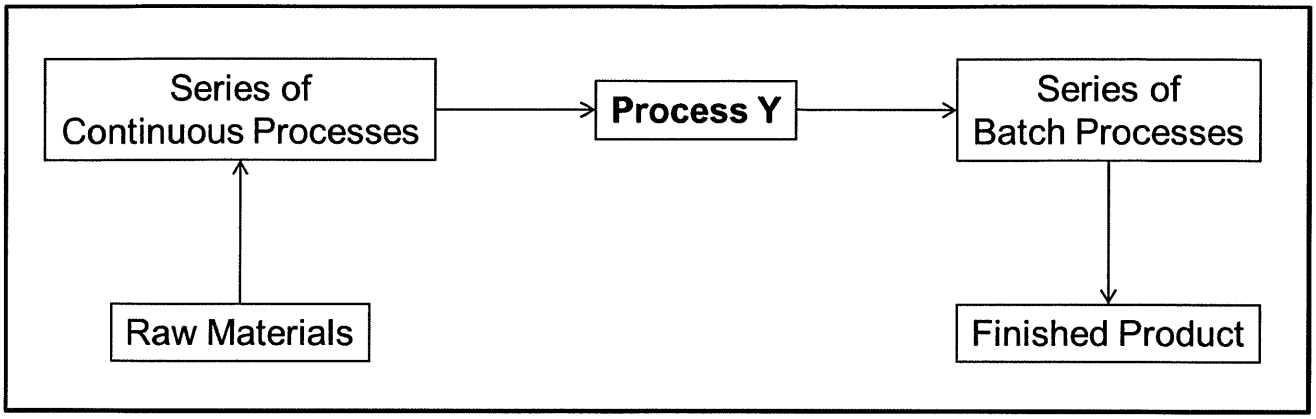
Figure 1- Simplified Product X Flow



2.1.2.1.2 Process Y

Process Y is an intermediary step in the production of product Y shown in Figure 2. It is the point in the production of product Y where the process goes from primarily a continuous process to primarily a batch process. Process Y consists of a continuous transportation step, a holding step, and a value added batch step.

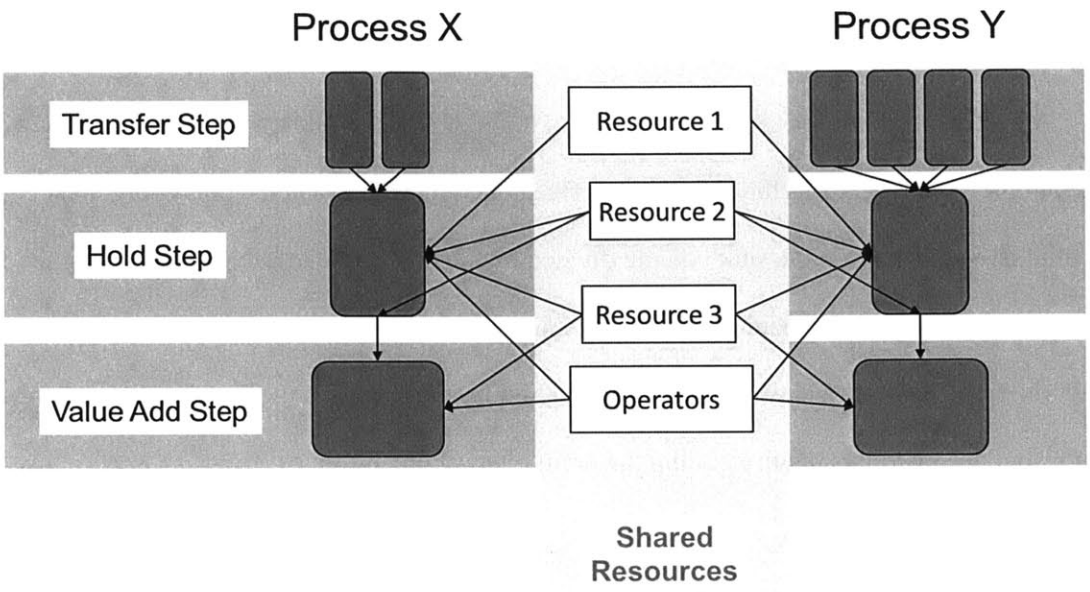
Figure 2 – Simplified Product Y Flow



2.1.2.1.3 Cross Functional Nature

Process X and process Y rely on many of the same resources including cleaning equipment, operators, and raw material inputs. These shared resources contribute to complex scheduling requirements. These scheduling requirements can take the form of sequence constraints or capacity constraints. An example of a sequence constraint is process X requiring a cleaning resource following the completion of a cycle. Because process Y uses the same cleaning resource after its cycle the two processes must be spaced a sufficient number of hours apart to ensure the cleaning resource is not required by both processes at the same time. A capacity constraint example is the operators who perform the manual sequences of both processes. The work content of each process has periods of heavy manual activity and low manual activity. If the heavy manual activity periods of both processes overlap, the number of operators available becomes a capacity constraint. These shared resource relationships mean the performance of one process directly impacts the performance of the other. Figure 3 below demonstrates the coupled nature of process X and process Y.

Figure 3 - Process X and Process Y Interactions



In Figure 3 the horizontal shaded bars indicate steps in process X and Y. The shapes aligned vertically under the process X and Y headings represent specific process equipment. The resources between the processes are shared. The arrows indicate product flow within each process and resource interaction where they connect a resource to process equipment.

2.1.2.1.4 Process Overview

In both processes the transfer step is continuous. This is due to the fact that all production upstream of process X and process Y is continuous. Upstream processes run for months at a time for product X and product Y at fixed rates. The rate of the continuous step in process X is different than that of process Y because of different upstream rates. Product exiting the transfer step fills inventory locations in the hold step. Inventory capacity for each process is fixed based on installed tank capacity. Process X tank capacity is smaller than process Y tank capacity. The value add step is a batch process that empties the product stored in inventory tanks. The relationship between the continuous transfer step rate and the inventory space available in the hold step dictates a target cycle time for the batch value add

step. If the value add step takes longer than target it is possible for the inventory location capacity to hypothetically overflow as the continuous transfer step does not stop.

A useful metaphor for these processes is to think of a kitchen sink with a running faucet and a plugged drain. The faucet fills the sink at some fixed continuous rate and the drain plug must be pulled at some time interval based on the sink volume divided by the faucet rate to avoid overflowing the sink. This is essentially what is happening in process X and process Y. In our case however, we have two sinks of different capacity and two faucets running at different speeds. And, to complicate things, the shared resource constraints require pulling the drain plugs at precise times.

Process X and process Y have been in production at the manufacturing site in question for a sufficient time as to be considered stable from an operations standpoint. This means simply that the two processes are not in a startup environment. Recently however, both processes began a decline in performance as measured by total product produced, average cycle time, product lost, and adherence to production schedule. This negative change is the first topic addressed by this thesis.

2.1.2.2 Problem Statement

Process X and process Y have been missing specific performance targets. The value add step for each process does not consistently meet target cycle times and as a result full production potential is not met. The specific trends and performance data will be discussed in detail in section 2.4 of this document, but the change causes us to wonder what happened. Namely, why are process X and process Y failing to meet targets and what changes occurred leading to current state? What can be done in the short and long term to improve the performance of these processes?

2.1.3 Background Research

Genzyme operates in the biotechnology industry which presents unique challenges due to strict regulatory standards, complex products, and the importance of the medically necessary medicines they produce. However, many of the operations management concepts and relationships that apply to other

industries hold true for biotechnology. This section provides an overview of useful background research related to capacity, variability, and process performance. Namely that variability in any system degrades overall performance and variability must be accounted for in some type of buffer. Buffers can include process time, capacity, or inventory.

2.1.3.1 Process Management

It is the job of the operations function in any organization to design, understand, and improve processes.[17] In a static environment this role is fairly simplistic requiring little oversight. As supply chains, companies, industries, and the environment become more complex and competitive, operations managers have to deal with the impact of uncertainty.[18]

2.1.3.2 Little's Law

A commonly referenced theorem useful for understanding basic relationships in operations was first developed by John Little[19]. Known as Little's law it is a foundational building block of queuing theory. The law states that in any steady state system the number of units in the system is equal to the expected time a single unit will remain in the system multiplied by the arrival rate of units into the system:

Equation 1 - Little's Law

$$L = \lambda W$$

where L = *expected number of units in the system*

W = *expected time spent by a unit in the system*

$1/\lambda$ = *expected time between two consecutive arrivals to the system*

[17] (Klassen & Menor, 2007)
[18] (Klassen & Menor, 2007)
[19] (Little, 1961)

The usefulness of the relationship between rate (λ), time (W), and buffer (L), comes from the ability to calculate one factor once the other two are known. For example if we know the average number of customers in a bank and the arrival frequency we can determine the average amount of time a customer will spend in the bank. This law is adaptable to many situations and can be rewritten as a relationship between inventory, process rate, and process time:

Equation 2 - Little's Law - Manufacturing Notation

$$I = r_p W$$

where I = *expected number of units in inventory*

W = *expected time spent by a unit in process*

r_p = *mean production rate*

This expression is more relevant to manufacturing situations. In the general case the term "I" accounts for work in process, the term "W" represents total system processing time and the term "r_p" the number of units processed per unit time.[20]

While Little's law provides a useful basis for understanding a process it assumes a steady state system. In order to apply this thinking to systems with variability in production rates and arrival rates we turn to the general case of a G/G/1 queue. The G/G/1 model assumes an arbitrary arrival rate, an arbitrary processing rate and a single server. In other words, it provides the most basic case. For background information on queuing theory please see Gross and Harris (1998) or Hopp and Spearman (2001). Kingman (1961) derived the formula for expected process time in a G/G/1 system with variable arrival rate and processing rate:

[20] (Klassen & Menor, 2007)

Equation 3 - Process Time for a Variable G/G/1 System

$$W = \left(\frac{\rho}{1-\rho}\right)\left(\frac{cv_d^2 + cv_p^2}{2}\right)\frac{1}{r_c} + \frac{1}{r_c}$$

where

W = *expected time spent by a unit in process*

ρ = *utilization*

cv_d = *coefficient of variation for demand (arrival rate)*

cv_p = *coefficient of variation for process*

r_c = *process capacity rate*

Substituting the expected process time from the G/G/1 system into the Little's law formula and solving for inventory we see that:

Equation 4 - Inventory in a Variable G/G/1 System

$$I = r_p\left(\frac{\rho}{1-\rho}\right)\left(\frac{cv_d^2 + cv_p^2}{2}\right)\frac{1}{r_c} + \frac{r_p}{r_c}$$

We can drop the last term by assuming that inventory is much greater than one and utilization is less than one leaving us with an approximation for inventory that relates utilization and process variability (internal and external):

Equation 5 - Inventory as a Function of Utilization and Variability

$$I \cong \left(\frac{\rho}{1-\rho}\right)\left(\frac{cv_d^2 + cv_p^2}{2}\right)$$

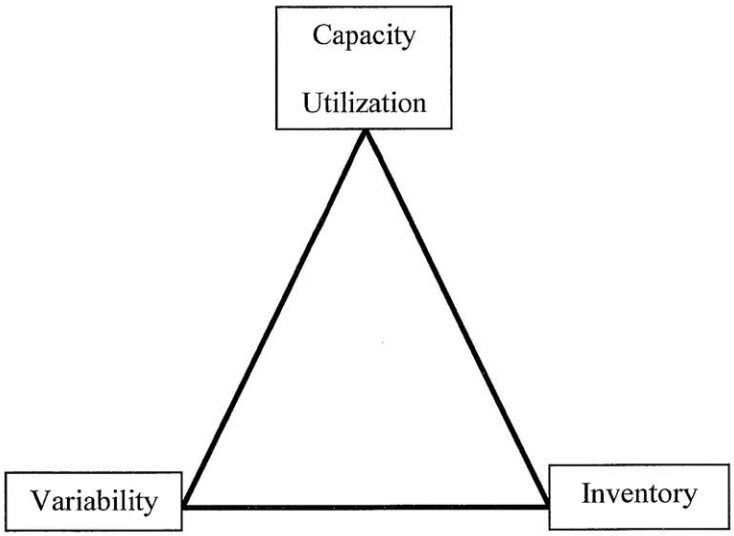
This last relationship links variability, capacity (utilization), and inventory in a non-linear form showing us the tradeoff that a manager must make either explicitly or implicitly to optimize the performance of his or her system[21].

2.1.3.3 Variability Tradeoffs

Hopp and Spearman (2004) note that increasing variability always degrades the performance of a production system including throughput, lead time, customer service, quality and others. They go on to state that variability in a production system is buffered by some combination of inventory, capacity, and time. This trade-off is depicted in Figure 4, the process management triangle.

2.1.3.4 The Process Management Triangle

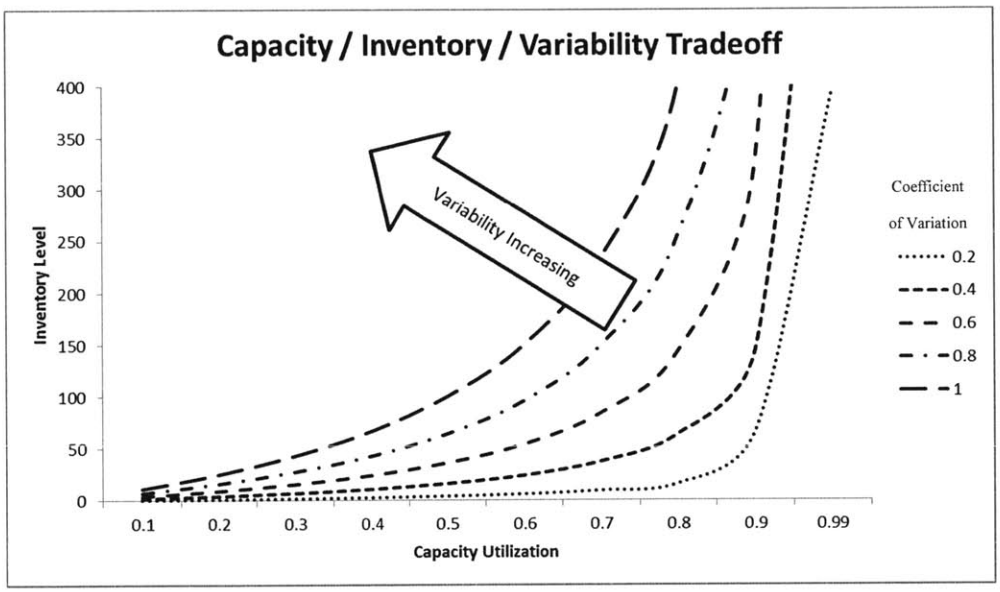
Figure 4 – The Process Management Triangle



[21] (Klassen & Menor, 2007)

In this triangle, process time represents the performance of the process and is held constant. A change in one point on the triangle will impact at least one of the other points. If demand (external variability) spikes in a single period either inventory will be drawn down, or spare capacity will be put to use in order to maintain the same service time. If inventory or spare capacity are not available, the performance of the system will decrease. These tradeoffs are shown graphically in Figure 5.

Figure 5 – Capacity Inventory Variability Tradeoff



Each line on the chart represents a different level of process variability. The numbers in the legend are the coefficients of variation used in Equation 5 to calculate the curve. The chart shows that when variability is low we can achieve a high level of capacity utilization with low inventory. As variability increases we are forced to either carry additional inventory, reduce utilization, or both to maintain performance. The time dimension is not shown on this chart but can be substituted for either capacity or inventory. If we are unwilling or unable to decrease capacity utilization or increase inventory, we can buffer the effects of variability by increasing the amount of time it takes the process to deliver; in effect lowering the customer service performance. The chart shows when capacity utilization is low, variability does not have a significant impact on inventory. However, if one were to increase capacity utilization for a variable process the negative impact to inventory or process time would be significant.

This key decision of how to address internal and external variability is a core principle of process management. The process management triangle is the framework used in this document to analyze the change in performance for process X and process Y. In the next section of this document utilization rates and variability for both processes are reviewed to establish trends from when the processes were meeting targets through the current state.

2.2 Method

The method for understanding process X and process Y performance includes four steps:

1. Understand and characterize the current processes
2. Collect data from historical records
3. Analyze the data looking for trends
4. Apply the process management triangle to explain changes

2.2.1 Understanding and Characterizing the Current Process

Process X and process Y are completed using a variety of equipment, computer systems, personnel, documents, and testing equipment. The process X batch step cycle time target is 36 hours while the batch step cycle time target for process Y is 24 hours. Because of the complexity of the systems and the duration of the process the author spent considerable time observing the work directly and interacting with operators, supervisors, and support workers who staff the process. In total process X was observed in its entirety six times and process Y was observed seven times. This was completed over numerous shifts working with multiple work crews to understand what was happening.

The highly automated nature of the manufacturing process requires precise measuring and metering equipment. Information such as holding tank level, pump speed, vessel temperature, pipe pressure, and many other metrics are available real-time to support the process as well as cataloged in a historical tracking system. The combination of direct observation, documented work instructions, and automated system information enables analysis of current and past process performance.

Process X and process Y have natural sub-steps. These steps are characterized by an observable beginning and end during which a specific function is performed. While the duration and specifications of each step are different for process X and process Y, the functions are the same. Table 1 describes each step and gives a brief description. Each step is also classified as automated, meaning controlled by the equipment and information technology infrastructure and whether it is cross-functional, meaning

requiring staff from multiple groups to collaborate. In the example of the documentation review members of quality assurance and manufacturing departments must work together to complete the task.

Table 1 - Process Steps

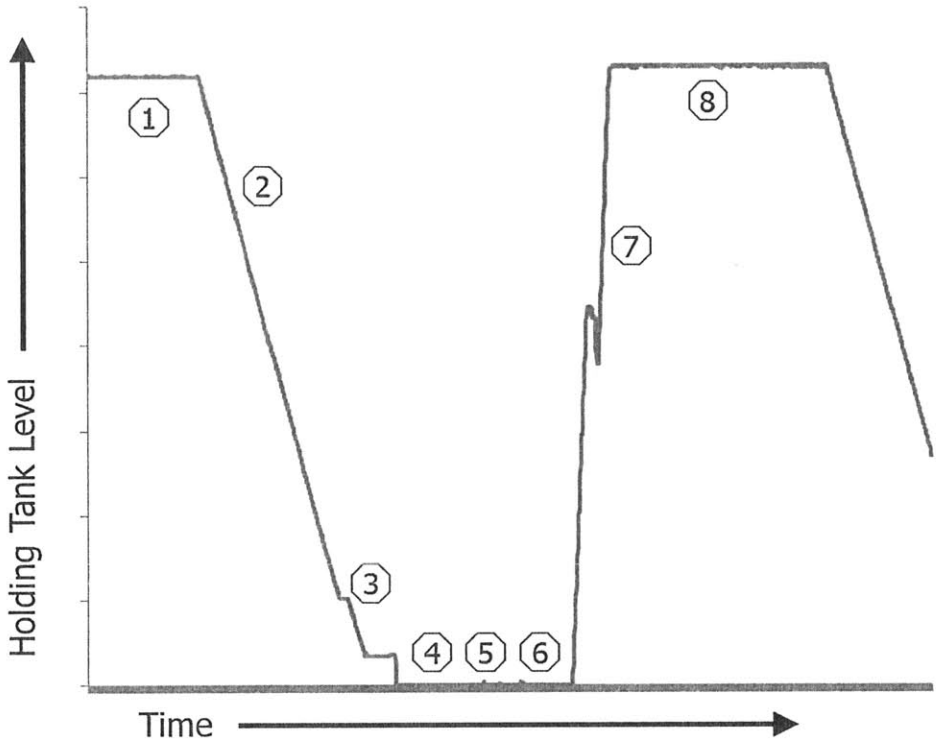
Step	Description	Automated	Cross-Functional
Step 1	Quality Assurance documentation review	No	Yes
Step 2	Product transfer out	Yes	No
Step 3	Tank drain	No	No
Step 4	Wait for cleaning	No	No
Step 5	Cleaning	Yes	Yes
Step 6	Wait for product transfer in	No	No
Step 7	Product transfer in	Yes	No
Step 8	Wait for material replenishment	No	Yes

These step designations were selected by the author to achieve a level of granularity sufficient for analysis and having start and end points discernable from the historical data sources. While it is possible to analyze each process in more resolute detail through time studies and direct observation we would not be able to compare the performance of prior time periods. Breaking down the process in the manner described allows us to use historical data to compare past performance.

Steps four, six, and eight include a waiting component. In some instances these waiting periods occur due to lack of availability of shared resources or delays in order to synchronize with other supporting functions or processes. The waiting steps in these cases can also help maintain consistency. Process X and process Y have defined cycle time targets, therefore performing too quickly can have negative consequences as can performing too slowly. It is important to note that the process is a closed loop. After step eight completes the process is ready to begin again with the quality assurance documentation review of step 1.

An example of the process as it looks from automated data tracking information is presented in Figure 6. The graphic is a chart of readings from the level transmitter on the process Y holding tank. It shows the inventory of the tank over time.

Figure 6 –Visual Process Cycle



The chart indicates how the steps outlined in Table 1 refer to specific steps in process X and process Y. For example, step 1 ends when the level in the holding tank begins to drop indicating product is transferring out. Step 6 ends when the level in the tank increases sharply as more product is transferred in for the next cycle. Step 8 is the amount of time product remains in the tank starting with the end of the transfer in and ending with the start of transfer out. These process transitions repeat for each cycle. Identifying these milestones and comparing them to trends for multiple automated data collection devices made it possible to mine current data as well as existing archived historical data to understand changes to the process over time. Comparisons are then possible from run to run on a case by case basis or time period to time period on an aggregate basis.

The time period to time period comparisons are important because process X and process Y experience peak production phases. These peaks in production occur when upstream processes increase output periodically. A peak can last anywhere from fifteen to forty days. Product X and product Y peaks can occur independent of each other or they can overlap. During these peaks process X and process Y must increase their throughput to match the pace. This means the cycle time requirement during product peaks is most critical. Because these periods of peak production stress the system they are used as the basis for performance comparison in this analysis. If performance is sufficient during peaks it stands to reason problems will be minimized during non-peak production.

2.2.2 Collecting Historical Data

Once the process was characterized and a framework for analysis was established the next step was to gather historical automation data. Information including step task time, resource utilization rates, product produced, and product lost, was collected for six historical peak periods. To protect the confidentiality of the processes the specific dates are masked, but the peaks represent a period of several years. The data was collected using Excel based spreadsheet tools to extract information from the historical database. The raw data were then manually reviewed to determine the milestones discussed in the previous section. These milestones provided the task time for the steps that make up process X and process Y. Resource utilization data was extracted from the database in a similar fashion. For example, process data for a cleaning system was extracted for various peak periods to identify the amount of time the resource was in use. Finally, some information came from Genzyme reports including total product produced and lost for each period. With all of the data collected we are able to analyze the information to identify trends and comparisons.

2.2.3 Analyzing Data

The data analyzed in the next section focuses primarily on changes in process Y performance over time. During the six peak production periods the quantity of process X runs increased significantly

while the number of process Y runs remained relatively constant. This makes using the early peaks as a baseline for process Y more relevant.

Collecting data for process X and process Y yielded a significant amount of information. Recall the process management triangle framework described in section 2.1.3.4. It describes the necessity to account for variability in a buffer of time, inventory, or capacity utilization. As process X and process Y have fixed inventory capacity the relevant analysis focuses on variability and utilization. Starting with the first period, the following analysis was completed for process Y for each peak:

- Total process cycle time
- Total process cycle time variability
- Sub-step cycle time
- Sub-step cycle time variability
- Product lost[22]
- Schedule compliance

The cycle time metrics are a measure of total time elapsed from the beginning of one step or cycle to the beginning of the next step or cycle. The product lost value is a Genzyme measured and reported metric. Product is lost when total process cycle time exceeds target causing insufficient space in the work in process inventory location. In this situation the upstream process continues to operate while the inventory location is already full. The only option is to remove and scrap material until the work in process tank can be emptied. The schedule compliance metric is a measure of how many runs of process X or process Y were completed during the peak compared to how many should have been completed as a percentage. For example if a peak lasted 30 days and process Y has a target cycle time of 24 hours there should have been 30 runs of process Y. The schedule compliance figure in this case would be 100%. If only 20 runs of process Y were completed the schedule compliance would be 67%.

[22] The product lost metric in this analysis refers to lost work in process material and is not indicative of total process yield

In addition to the peak specific metrics there are other relevant pieces of data incorporated into this analysis. These values span multiple peaks or in some cases tell the story of utilization changes over the entire time period:

- Shared resource utilization
- Upstream process utilization

The utilization metrics apply to both process X and process Y. As we will see from the analysis the increase in process X runs had a significant impact on the utilization of the shared resources that both X and Y depend on.

This set of metrics allows us to benchmark process variability, process utilization, and process performance over time. Remembering that process X and process Y have fixed work in process inventory vessels we have all the necessary inputs to the process management triangle framework.

2.2.4 Applying the Process Management Triangle Framework

The final step in the methodology applied for this project is using the process management triangle to explain the findings from the data analysis and recommend an approach to improve performance. The results of this step are found in the discussion section of this document.

2.3 Data

As discussed in the previous section the peak periods of production for process X and process Y provide useful reference points to determine changes over time. In this section some of the data is displayed as pertaining to peak 1, peak 2, etc. To protect Genzyme confidentiality the specific dates will not be used but the peaks occurred over multiple years and are listed in sequential order with peak 1 as the earliest and peak 6 the most recent.

2.3.1 Variability

2.3.1.1 Cycle Times

Each of the tables below summarize cycle time metrics for steps in process Y during each of six production peaks described in the previous section. The average and standard deviation (Stdev) values are measured in hours. For example, step 1 in peak 1 averaged .9 hours per cycle with a standard deviation of .78 hours. The calculated coefficient of variation (CV) value is then listed on the next row for each step. The number is obtained by dividing the average of each step by its standard deviation. A higher number indicates more volatility and less predictability.

Table 2- Peak 1 – Process Y Cycle Time in Hours

	Step 1	Step 2	Step 3	Step 4	Step 5	Step 6	Step 7	Step 8	Total
Average	0.90	5.99	1.53	2.36	1.44	3.39	1.56	8.02	24.31
Stdev	0.78	0.64	0.49	1.46	0.18	1.85	0.27	3.48	3.86
CV	0.87	0.11	0.32	0.62	0.12	0.55	0.18	0.43	0.16

Table 3 - Peak 2 – Process Y Cycle Time in Hours

	Step 1	Step 2	Step 3	Step 4	Step 5	Step 6	Step 7	Step 8	Total
Average	2.88	6.03	1.93	2.20	1.45	3.54	1.72	8.14	25.00
Stdev	2.81	0.47	1.03	1.73	0.29	4.10	0.28	3.78	4.98
CV	0.98	0.08	0.54	0.79	0.20	1.16	0.16	0.46	0.20

Table 4 - Peak 3 – Process Y Cycle Time in Hours

	Step 1	Step 2	Step 3	Step 4	Step 5	Step 6	Step 7	Step 8	Total
Average	3.55	6.44	1.62	1.35	1.44	3.84	1.78	10.16	26.63
Stdev	3.65	1.14	0.42	0.97	0.17	6.65	0.51	4.30	7.40
CV	1.03	0.18	0.26	0.72	0.12	1.73	0.29	0.42	0.28

Table 5 - Peak 4 – Process Y Cycle Time in Hours

	Step 1	Step 2	Step 3	Step 4	Step 5	Step 6	Step 7	Step 8	Total
Average	3.47	7.10	1.59	1.67	1.55	2.74	1.73	16.46	32.84
Stdev	2.29	2.72	1.07	2.29	0.43	2.13	0.65	10.81	11.74
CV	0.66	0.38	0.67	1.37	0.28	0.78	0.38	0.66	0.36

Table 6 - Peak 5 – Process Y Cycle Time in Hours

	Step 1	Step 2	Step 3	Step 4	Step 5	Step 6	Step 7	Step 8	Total
Average	1.94	7.24	1.61	1.38	2.08	4.49	2.10	14.69	33.86
Stdev	1.18	1.43	0.42	1.91	0.10	4.41	0.57	6.86	9.75
CV	0.61	0.20	0.26	1.39	0.05	0.98	0.27	0.47	0.29

Table 7 - Peak 6 – Process Y Cycle Time in Hours

	Step 1	Step 2	Step 3	Step 4	Step 5	Step 6	Step 7	Step 8	Total
Average	2.57	6.69	1.39	1.41	1.90	8.06	1.88	16.52	40.72
Stdev	1.70	0.74	0.36	0.80	0.23	5.46	0.78	5.77	12.85
CV	0.66	0.11	0.26	0.56	0.12	0.68	0.42	0.35	0.32

Figure 7 - Process Y Cycle Time

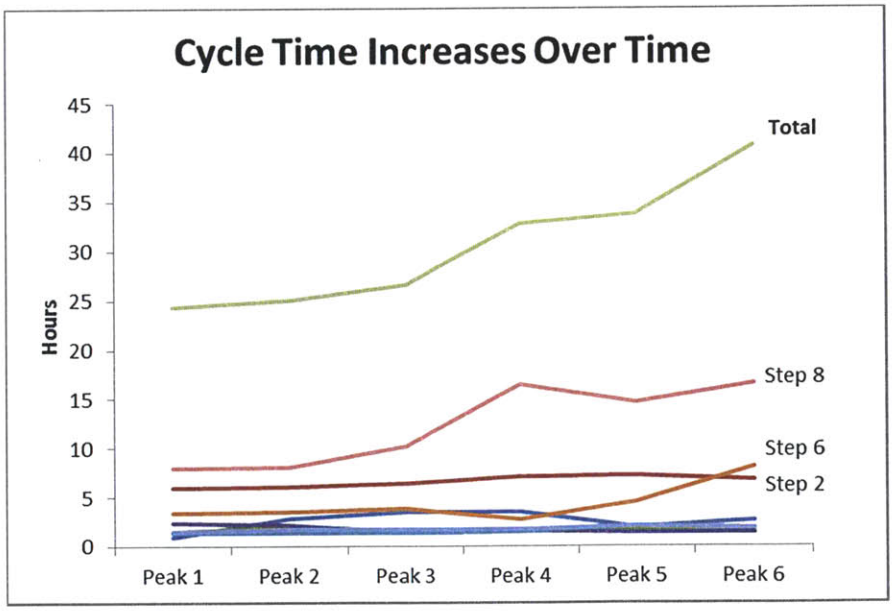
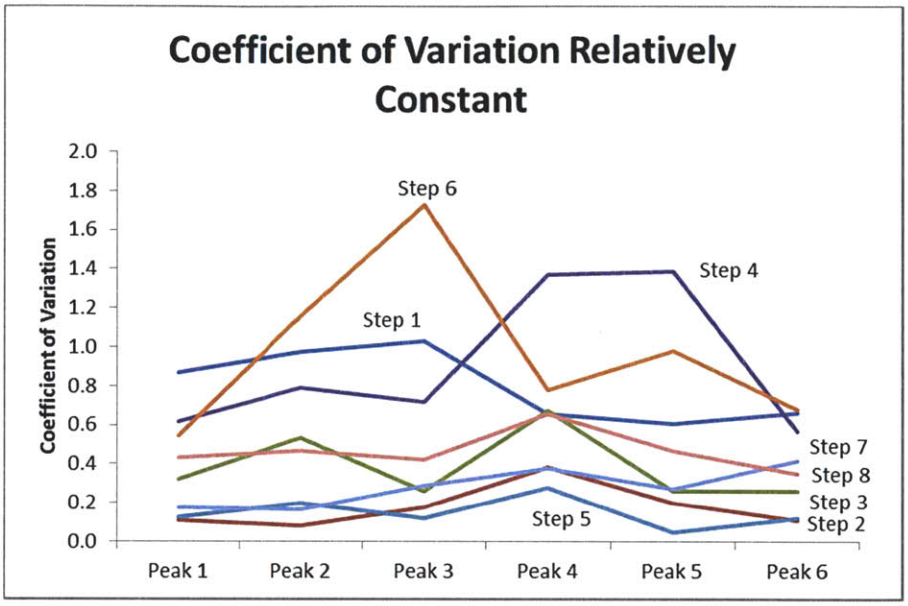


Figure 8 - Process Y Coefficient of Variation



2.3.2 Utilization

2.3.2.1 Upstream Utilization

Figure 9 and Figure 10 below show utilization of upstream equipment feeding process X and process Y. The value is a measure of total days of output in each year divided by 365. For illustration, in the first period, upstream equipment produced product X for 80 out of 365 days yielding a utilization of 22%.

Figure 9 - Process X Upstream Utilization

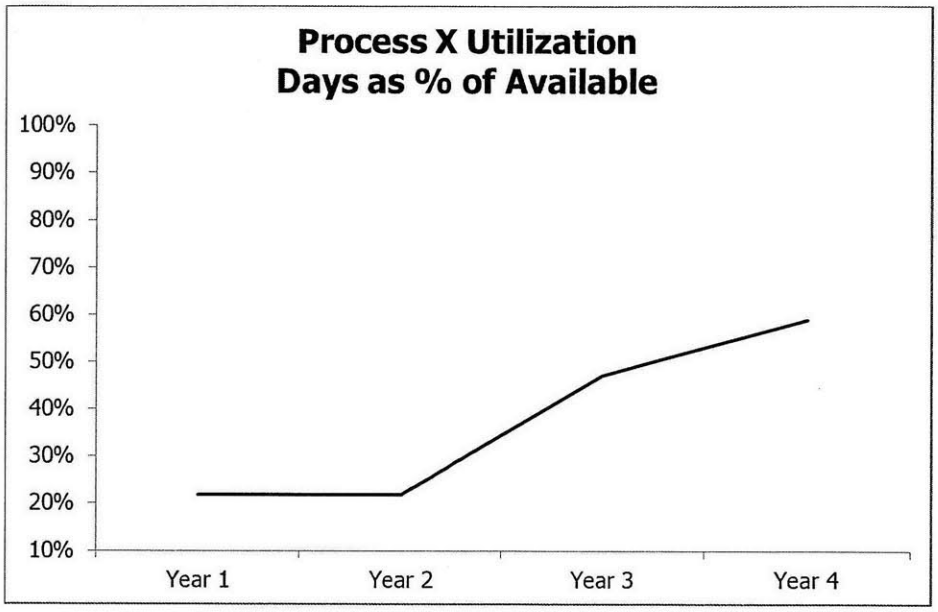
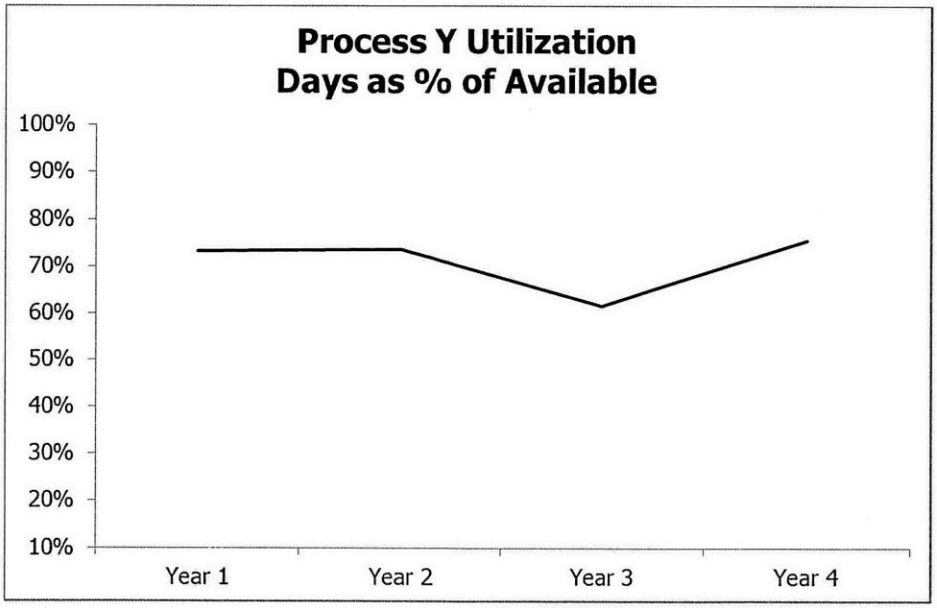


Figure 10 - Process Y Upstream Utilization



2.3.2.2 Shared Resource Utilization

Figure 11 - Shared Cleaning Resource Utilization

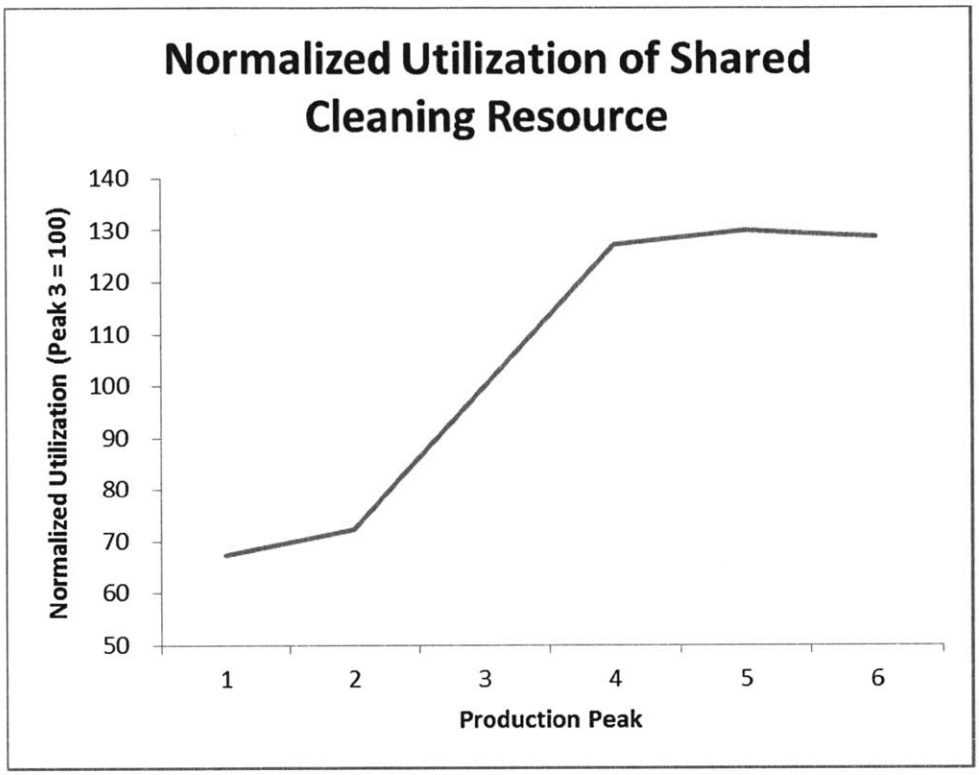


Figure 11 depicts the change in relative utilization of a shared cleaning resource. As the trend shows, relative utilization during peaks 1 and 2 was only about 70% of the utilization during peak 3. In contrast, utilization of the cleaning resource during peaks 4, 5, and 6 is 130% of the utilization during peak 3. For this example utilization is calculated as the amount of time the cleaning system is in use over the total available time of the system.

2.3.3 Process Performance

2.3.3.1 Schedule Compliance

Table 8 below shows process Y schedule compliance for each of the six production peaks. Schedule compliance is calculated by dividing the number of runs completed in a peak by the number that should have been completed.

Table 8 - Process Y Schedule Compliance

Peak	Target Runs	Actual Runs	Compliance
1	58	56	97%
2	75	64	85%
3	78	71	91%
4	67	49	73%
5	57	39	68%
6	37	24	65%

2.3.3.2 Product Loss

Table 9 below lists product Y losses during each production peak. This represents a quantity of work in process material that was scrapped due to process Y.

Table 9 - Process Y Product Loss

Peak	Product Loss*
1	0.0
2	0.0
3	6.8
4	32.8
5	32.1
6	20.8

*The product loss value is masked to protect Genzyme proprietary data. The relative value demonstrates the change in magnitude from peak to peak but does not indicate an actual value.

2.4 Discussion

2.4.1 Decreased Process Performance

Process Y performance shifted in a negative direction from the early production peaks to the most recent based on schedule compliance and product loss. Schedule compliance as defined in this study is the percentage of process Y runs that occurred during a peak compared to how many should have occurred based on the target cycle time. As we see in Table 8, schedule compliance shifted noticeably between peaks 1-3 and peaks 4-6. The longer it takes to run process Y the fewer cycles can be completed during a peak period. Figure 7 shows the overall increase in total cycle time from peak 1 through peak 6. Peaks 1 through 3 averaged close to 25 hours per cycle while peak 4 increased to 33 hours, peak 5 to 34 hours, and peak 6 over 40 hours. This increase in total cycle time was a major contributor to the decrease in schedule compliance.

Because of longer cycle times and missed process runs product losses also increased. Table 9 shows the increase in losses from no product loss in peaks 1 and 2 to some loss in peak 3 and escalated losses in peaks 4 through 6.

In order to understand the negative shift in performance we need to examine variability and capacity utilization trends.

2.4.2 Cycle Time Variability

Over the course of multiple peaks changes were made to some sub-step process work content. For example in some cases cleaning time duration was increased, additional quality checks were added, and operators were asked to perform extra procedures. This explains some of the increase in sub-step cycle times for step 8 and step 6 most notably. For all other sub-steps the cycle time remains relatively constant from peak to peak. Figure 8 shows the value of the coefficient of variation for each sub-step at each peak. It is interesting to note that while there are significant swings for some sub-steps from peak to peak there are no upward or downward trends. Each sub-step maintains its relative consistency or

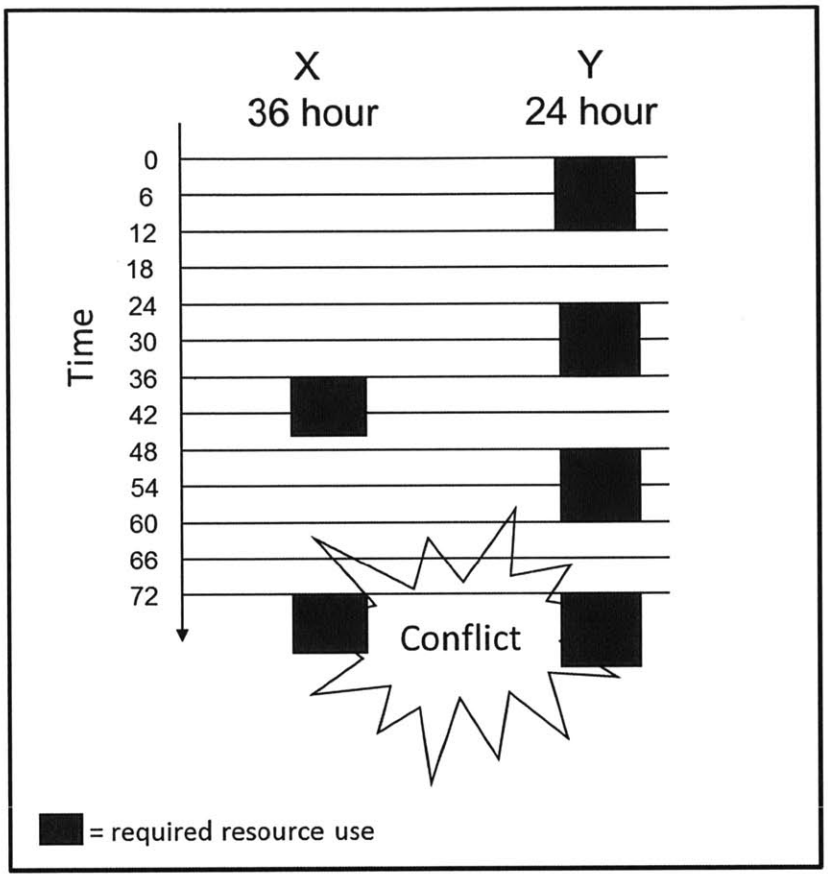
inconsistency throughout the time period included in the study. Some steps show significant variability with coefficients of variation over 1.5.

2.4.3 Variability Caused by Resource Conflicts

During the data collection and process characterization process it became apparent that some of the shared resource conflicts were a cause of variability. When process X and process Y are both at peak production rates, process X has a target cycle time of 36 hours and process Y has a target of 24 hours. This difference in run rate causes periods of two processes requiring the same resource.

The example below in Figure 12 represents an example of the conflict graphically. Assume process X runs at time 36 and every 36 hours thereafter. Process Y starts at time 0 and every 24 hours thereafter. The shaded boxes represent the amount of time during each cycle that a particular cleaning resource is required to execute each process. The area where the boxes overlap is a conflict that must be addressed by a management choice to delay one process or the other. These delays create variability from the scheduled plan.

Figure 12- Shared Resource Conflict Example



2.4.4 Utilization Increases

The data clearly demonstrates that utilization has increased mostly due to process X upstream changes. This change puts a strain on shared resources leading to less availability for process Y. The data also shows a change in utilization for process Y due to increases in sub-step cycle times. Additional time is necessary to extended cleaning cycles, meet additional quality requirements, and other changes. This increase in work content using the same existing resources increases overall utilization.

2.4.4.1 *Higher Throughput*

Figure 9 in the data section represents the amount of time equipment upstream of process X is producing product X. This upstream production dictates the run rate required of process X. As the chart shows, upstream production for process X increased from approximately 20% of available time in Year 1 to nearly 60% of available time in Year 4 – a three times increase. Figure 10 is the same data for upstream production of product Y. Product Y upstream production was approximately 70% in Year 1 and Year 4.

2.4.4.2 *Increased Work Content*

The steps that make up process X and process Y did not go through fundamental changes during the time between peak 1 and peak 6; however, work content was added to some steps. Table 10 compares the average time for each step during peaks 1 to 3 and peaks 4 to 6. As the data shows the time required to complete step 6 and step 8 increased dramatically. While it is not clear from the historical data how much of the time increase is due to additional work as opposed to waiting for resources, because the increases are in steps 6 and 8 and not distributed across all steps, it is clear the change was specifically within those steps.

Table 10 – Process Y Sub-Step Cycle Time Shifts

	Step 1	Step 2	Step 3	Step 4	Step 5	Step 6	Step 7	Step 8	Total
Peak 1-3	2.44	6.15	1.69	1.97	1.45	3.59	1.69	8.77	25.32
Peak 4-6	2.66	7.01	1.53	1.49	1.84	5.10	1.90	15.89	35.81
Delta	0.22	0.86	-0.16	-0.48	0.39	1.50	0.21	7.12	10.49

2.5 Conclusion

Recent events at Genzyme demonstrate not just the importance of operational performance, but also the necessity to develop and manage robust systems with feedback mechanisms that help managers focus on the most important areas for improvement. The focus of this research effort is to understand the key performance drivers of two Genzyme production processes and help managers make the best decisions to improve them. In previous sections we reviewed the two production processes, used a methodology relating utilization, inventory, and variability to show the performance of process Y had declined, and attributed this change to an increase in utilization without offsetting adjustments to variability or other system buffers.

A number of key facts present in the data demonstrate how process X and process Y utilization and variability measures performed from early to late production peaks. The process Y sub-step variability fluctuated from peak to peak, but did not exhibit any upward or downward trend. The utilization of shared resources as well as upstream process X equipment increased significantly from earlier peaks to later peaks. And finally, some process Y sub-step average cycle times increased over time. These changes tell us that the amount of work demanded of the process X and process Y system increased substantially over time while the supporting resource capacity was not increased at a rate that maintained constant utilization levels. During these changes the underlying operational processes exhibited no reduction in cycle time variability. These changes demonstrate a system in two very different states. Early production peaks are measurably different from late production peaks with relation to demands on the overall system. In accordance with the process management triangle discussed in section 2.1.3.4, an increase in utilization without a corresponding decrease in variability or increase in inventory will result in degraded process performance as measured by time.

The obvious question that arises from this analysis is what should be done to improve the performance of process Y? The following section proposes a logical next step. The variability in cycle time arising from shared resource constraints between process X and process Y is a known cause of poor

performance. Because we know what target cycle time is necessary at any given time for each process based on upstream production rates we can determine the optimal shared schedule for process X and process Y in any given scenario. The next section presents a method for creating a shared resource scheduling model to reduce system variability and examines the projected performance improvement through modeling.

3 Analysis 2 – Shared Resource Scheduling

3.1 Background

In the previous analysis, process X and process Y were introduced as critical operations taking place in an existing Genzyme biopharmaceutical production facility. They were described as a system of people, equipment, and information necessary to complete a step in the production of product X and product Y. The first analysis shows that over time the performance of process Y declined due to a number of reasons:

- **Utilization Increases** - The number of process X runs increased due to increased upstream production of product X. This caused higher utilization rates and less availability of shared resources used by both process X and process Y. Additionally, work content associated with some sub-steps in process X and process Y increased from early to late production peaks.
- **Variable Cycle Times** - The combination of variability already present in process Y with less resource availability resulted in increased total cycle times.
- **Resource Conflicts** - The target cycle times of 36 hours for process X and 24 hours for process Y at peak production rates create conflicts as both processes eventually require the same resource at the same time.

While all of these causes require solutions this section focuses on resolving the shared resource conflicts. In short, what can be done to minimize the impact of shared resources while maintaining regulatory requirements? The analysis in this section provides options to deal with shared resources between process X and process Y. The method section presents possible production scheduling alternatives as well as describes how costs and benefits were calculated for each scenario. The data section lists each scenario with projected costs and benefits. The discussion scenario makes a case for the

best possible option given the trade-offs required. Finally, the conclusion section connects the analysis in this section to the overall goal of understanding and improving the process X and process Y system. It also leads into the final section of this thesis – recommended next steps as well as applications outside of process X and process Y.

3.2 Method

Prior to the introduction of this research project process X and process Y were scheduled as independent operations. Historically, when utilization rates were lower, this assumption did not lead to negative consequences. However, now that production has increased, resource conflicts cause problems. To understand how each processes impacts the other it is important to understand the interaction between process X and process Y and their respective upstream operations. The upstream operations and equipment for product X and product Y are independent of each other, but they have a significant impact on process X and process Y respectively.

Recall Figure 1 depicting a simplified production flow for product X. Continuous upstream operations feed process X. These upstream operations have two components that fluctuate over time. One is the volume of product being passed to process X. The second is the activity of product being passed to process X. Activity can be thought of as the density of product contained in a liter of work-in-process material. A common measurement for this activity is units per liter. Therefore on a given day of upstream production, a volume of work-in-process material at a measured activity level is transferred to process X. Process X must then be completed at a rate dependent on the amount of material it receives from upstream production. In the case of process X the volume of material is the critical factor. Once a certain quantity of liters has been transferred, process X must complete to keep the flow of product X uninterrupted. For process Y, the units produced by upstream systems determine the rate required. The next section illustrates these relationships in greater detail.

3.2.1 Process X and Process Y Cycle Time Determinants

The charts on the following page show the relationship between three key characteristics of product X upstream production. All three graphs have synchronized x-axis values to highlight the interactions over time. Figure 13 shows how the output in units per day changes over time. In this example using masked data, units per day production peaks are defined graphically. Figure 14 shows product X upstream production per day in liters. Compared to the units per day graph, this chart shows a binary function of output in that the upstream operations are producing a fixed volume per day or none at all. Finally, Figure 15 shows the cycle time target for process X based on upstream production rates. As the graphs indicate, process X is tied to the volume of output from upstream operations, not the units of output. Process X must complete at the target cycle time otherwise inventory locations that separate upstream production from process X will not be sufficient. Regardless of upstream production rates process X has the same work content each time it is performed. The unit per liter value is important because it determines the relative value of in-process material at any given time. Product lost during higher unit per liter production days is more costly than that lost during lower unit per liter days.

Figure 13 - Product X Upstream Output - Units

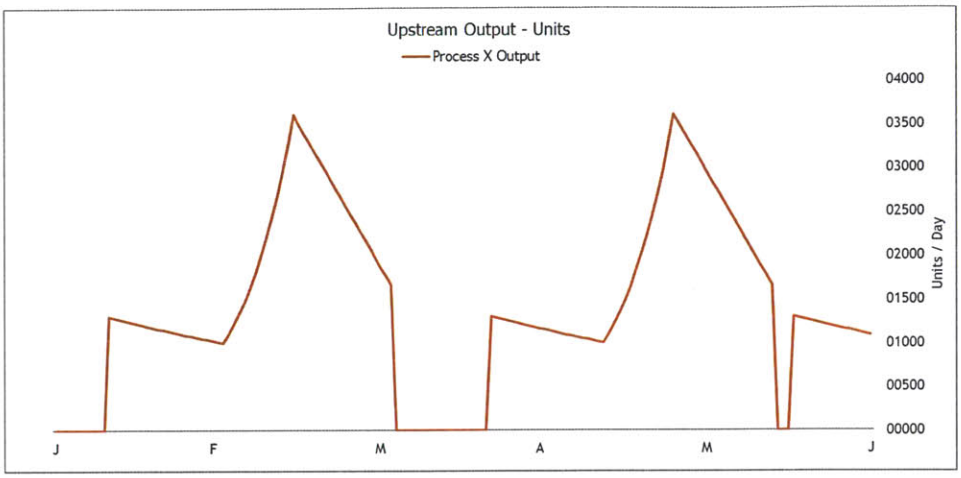


Figure 14 - Product X Upstream Output - Liters

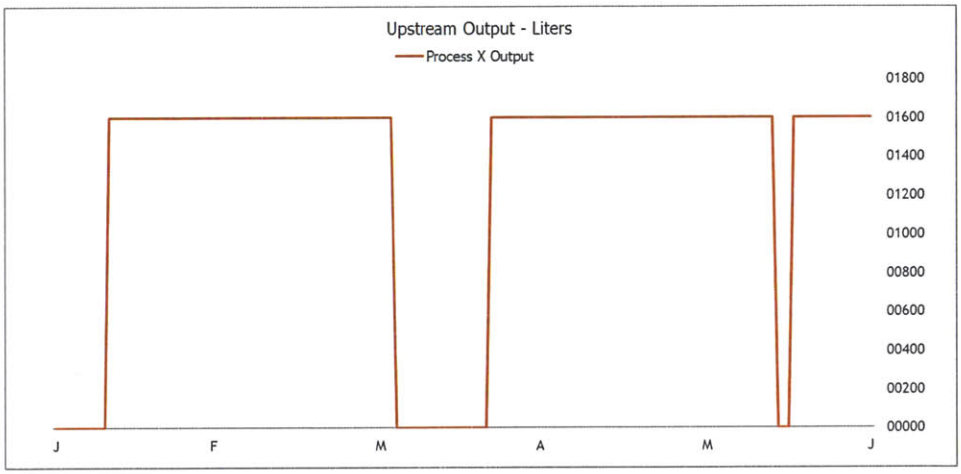
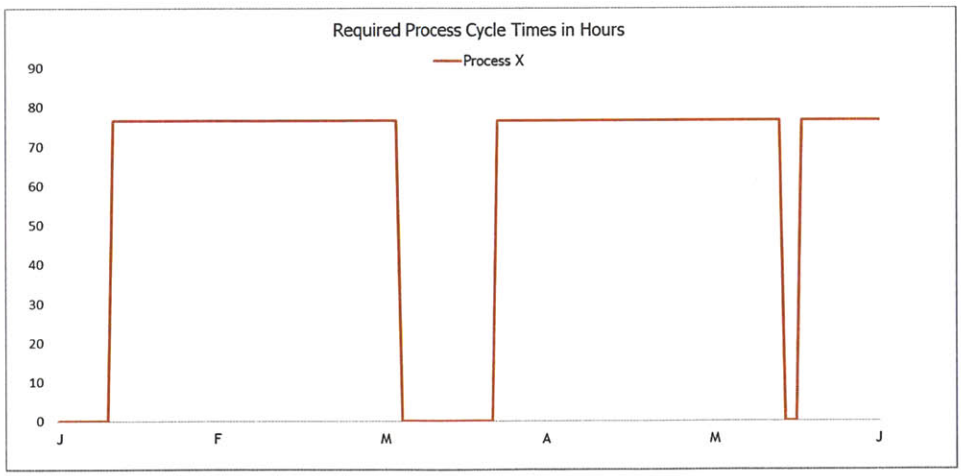


Figure 15 - Process X Target Cycle Time



While process X cycle time targets are dictated by upstream production volume, process Y cycle time targets are determined by product Y upstream unit per day values. The three figures on the next page reveal upstream output per day in units, liters, and the resulting cycle time targets for process Y. As in the prior section the x-axis of each graph is synchronized making it easier to see the interactions. Figure 16 shows units produced per day by product Y upstream systems. Figure 17 is a graph of liters produced per day. As opposed to the product X upstream process shown in Figure 14, product Y volume per day is not an on/off value instead fluctuating a great deal over time. Figure 18 shows the required cycle time that process Y must meet to avoid losing product sent from upstream operations and is essentially the inverse of Figure 16. While process X was tied to the volume of product coming from product X upstream systems, process Y is more closely tied to the units of production sent from product Y upstream systems. In the case of product Y, a slower than target cycle time would mean insufficient unit processing capacity and potential lost product.

Figure 16 - Process Y Upstream Output - Units

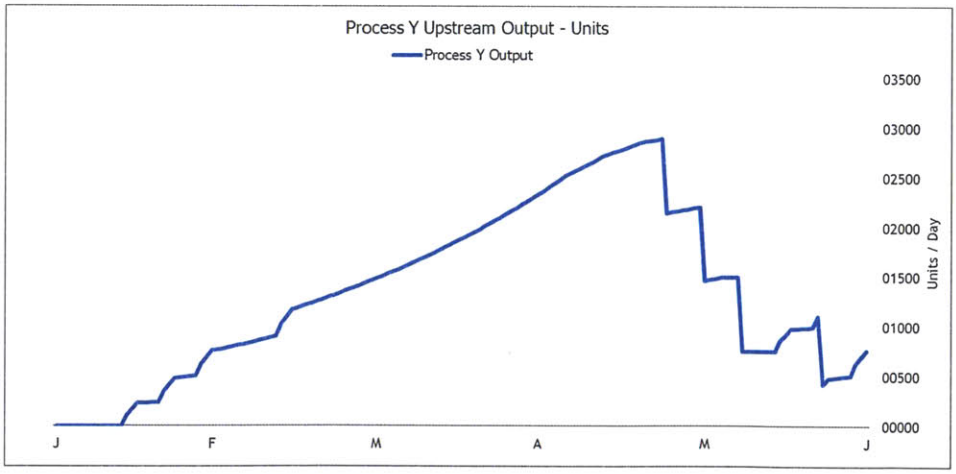


Figure 17 - Process Y Upstream Output - Liters

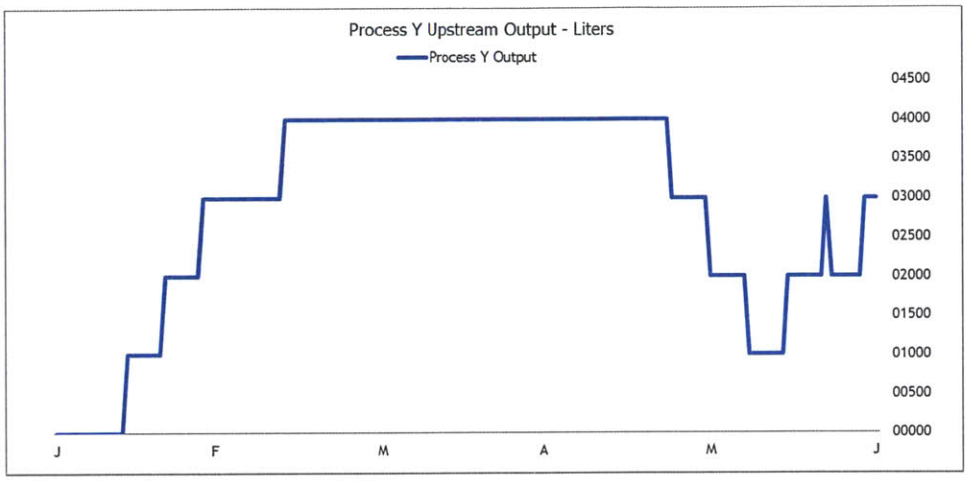
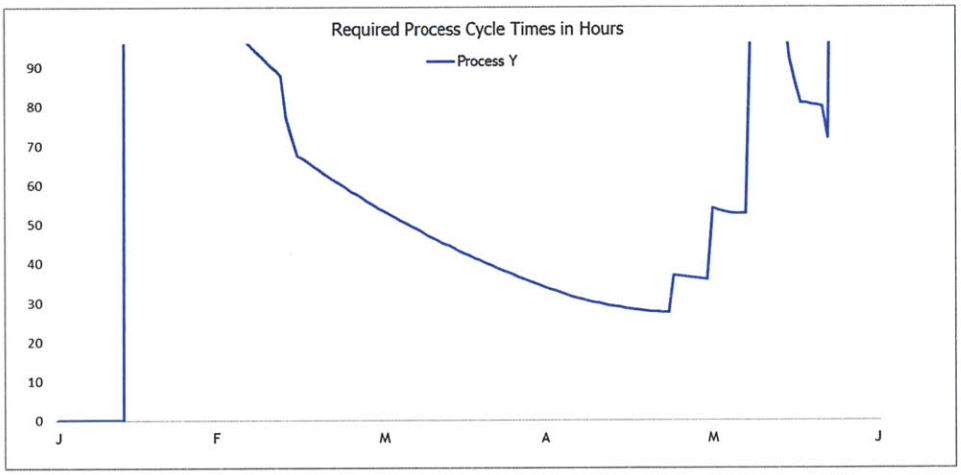


Figure 18 - Process Y Required Cycle Time



To summarize, process X cycle time targets are determined by the volume of production transferred from upstream product X systems while process Y cycle time targets are set by the number of units of product transferred from upstream product Y systems. This is important to understand because of the cause and effect relationship of upstream production quantities to process X and process Y run rates and the differentiation of volume importance for product X and unit importance for product Y.

3.2.2 Resource Conflict Occurrences

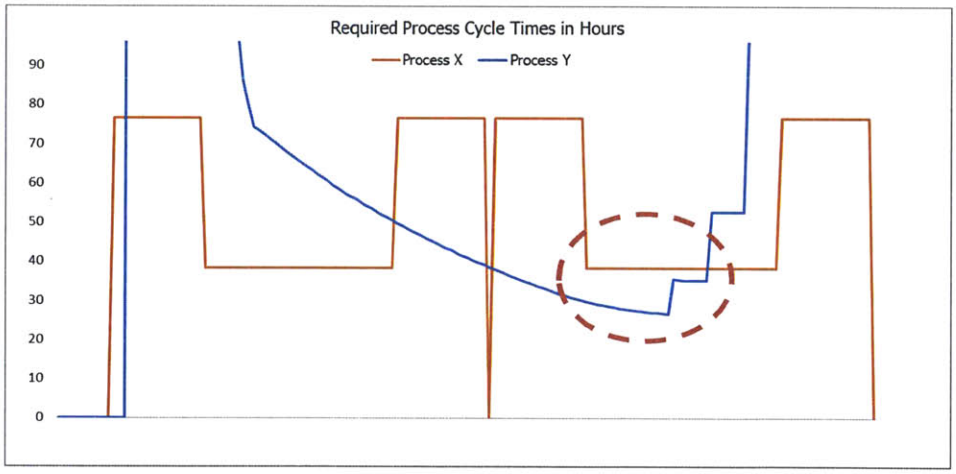
The next step in resolving shared resource conflicts in the process X and process Y system is to understand why they occur. We showed in the last section that upstream production rates dictate cycle

time targets for process X and process Y although in different ways. To illustrate, the next section reviews a period of resource conflicts during one of the production peaks reviewed in analysis one.

3.2.2.1 Resource Conflict During Production Peak

As upstream product X rates increased during production peaks 4, 5, and 6 as described in the first analysis section of this document, process X run rates increased accordingly. This increase caused periods of time with process X cycle time targets of 36 hours and process Y cycle time targets of 24 hours. These times are effectively overlapping production peaks. An example of overlapping peaks is presented in Figure 19 indicated by the dotted circle. During this time period (actual dates hidden due to confidentiality) process X cycle time target is 36 hours and process Y cycle time target hits a minimum of 24 hours. Times like this put the greatest strain on shared resources.

Figure 19 - Cycle Time Peak



In addition to the total demand placed on shared resources the incompatible cycle times present a sequence problem as described in section 2.4.3. When resources are required by each process for long periods of time, such as during a cleaning sequence, they will invariably and eventually need to use the same resource at the same time. The resulting conflict is a source of diminished performance and cycle time variability.

The upcoming data section examines various scheduling scenarios that lessen the shared resource problem. Each option requires the tradeoff of lower theoretical output in exchange for minimizing the potential for resource conflicts. In the discussion section the benefits and drawbacks of each scenario are reviewed with a final recommendation for the path forward in the conclusion section.

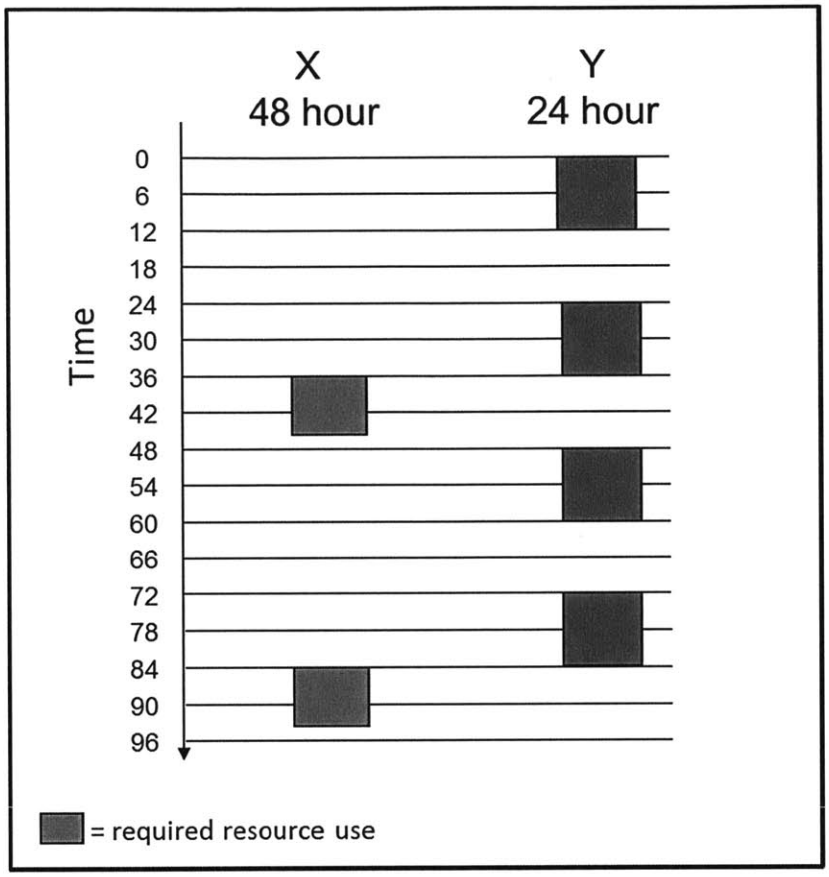
3.3 Data

The combination of shared resources and incompatible cycle times cause conflicts during peak production times resulting in lowered overall system performance. The optimal solution to this issue is the elimination of the shared resources allowing process X and process Y to operate independently. Unfortunately, this is not feasible in the short term. The capital costs, required process changes, and time necessary to implement and validate all of the changes warrant an interim solution. Given the requirement that process X and process Y must continue to run as a coupled system this section explores the various solutions which ultimately rely on common factor cycle times.

3.3.1 Common Factor Cycle Times

Resource conflicts occur between process X and process Y because of their shared resources and the incompatibility of their cycle times. Recall the depiction in Figure 12. As that example shows, processes which share resources and operate at uncommon factor cycle times will eventually converge resulting in a conflict. At peak production process X has a target cycle time of 36 hours and process Y has a target cycle time of 24 hours. This means the processes could be scheduled using common factor cycle times minimizing the potential for resource conflicts. For example, process X could run every 48 hours while process Y runs every 24 hours. Figure 20 illustrates the common cycle time concept using the same shared resource example from earlier in the document.

Figure 20 - Shared Resource Common Cycle Time



As we see in the example, a common factor cycle time eliminates this particular shared resource schedule conflict that arises when process X runs at 36 hours per cycle and process Y runs at 24 hours per cycle. The 36 hour cycle time for process X and 24 hour cycle time for process Y serve as a lower bound for the rate of either process; going faster is not a current option. Either process has the potential to go slower to mesh with the unaffected process. This gives management the choice of selecting one process to "lead" the other. By choosing a leader process and a follower process they are effectively maximizing the output of one process at the expense of the other. The follower process will be consciously given a slower cycle time resulting in lost product.

Working with a team of individuals that support process X and process Y the author developed two feasible scheduling scenarios. To create the scheduling options all potential constraints were examined for both processes simultaneously. Starting with the existing process X 36 hour cycle time and process Y

24 hour cycle time scenario the team determined the resource conflicts that commonly disrupt the process. Holding the schedule for one process constant the schedule for the other process was relaxed until there were no remaining conflicts. The result is a combined schedule that prioritizes process X and a combined schedule that prioritizes process Y. The process X leading schedule has a cycle time target of 36 hours for process X and 36 hours for process Y. The process Y leading schedule has a cycle time target of 24 hours for process Y and 48 hours for process X.

Evaluating these scheduling scenarios presented a challenge. Because each option represented knowingly sacrificing product of the follower process with the goal of maximizing product from the leading process, a simulation was conducted as a first order estimate of effectiveness. Using historical production peak data each scheduling option was tested for predicted lost product. While this is admittedly imprecise due to the inability to determine the amount of historical product loss attributable to shared resource conflicts as compared to other causes, it is directionally helpful. The values in the following data set tell us the cost of shared resource dependence between process X and process Y. They also help us see the potential benefit of being able to schedule the processes independently in the long term. Finally they provide some insight into the difference of the current state of dealing with resource conflicts as they occur, and the proposed scheduling solution which minimizes losses of one product at the expense of the other.

The following charts show masked product losses and simulated product losses under the two scheduling scenarios for production peaks 3, 4, 5, and 6. The simulations were created using spreadsheet software to calculate inventory inflows and outflows over time for actual peak production data. In each of the scheduling scenarios the cycle time targets cause insufficient inventory at peak production for the process in the follower role. The simulation tool calculates the amount of product lost due to this slower than target cycle time for the duration of the production peak.

Figure 21 - Actual Versus Simulated Schedule Product Loss

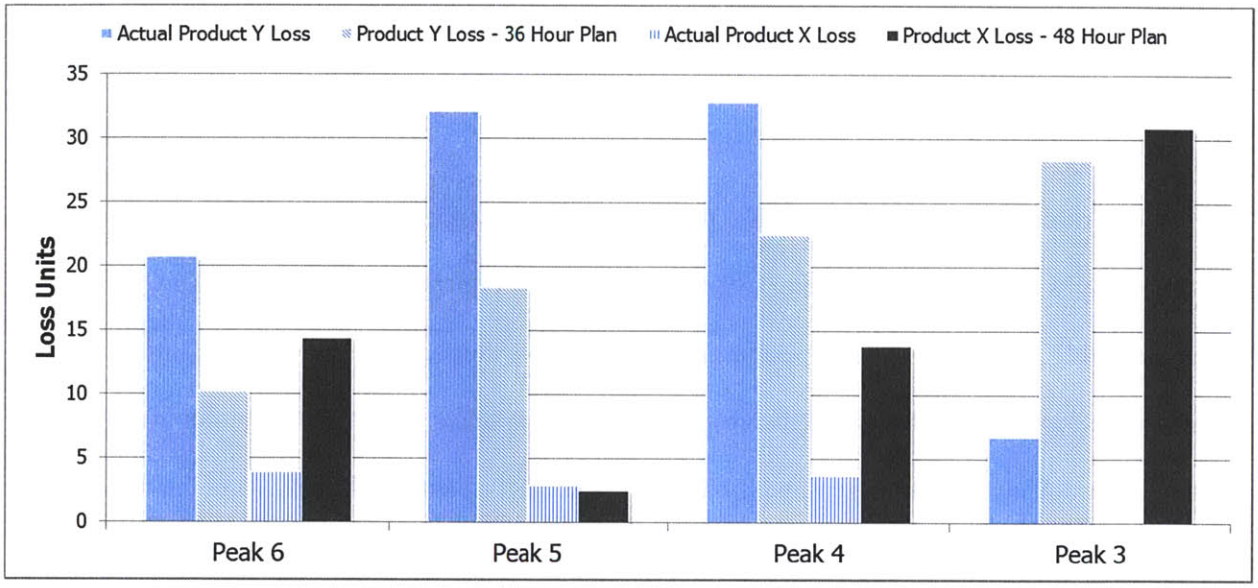


Table 11- Actual Versus Simulated Schedule Product Loss

	Peak 6	Peak 5	Peak 4	Peak 3
Product Y - Actual Loss	20.8	32.1	32.8	6.8
Product Y - 36 Hour Plan Loss	10.2	18.4	22.5	28.3
Product X - Actual Loss	4.0	2.9	3.7	0.0
Product X - 48 Hour Plan Loss	14.4	2.6	13.9	30.9

Figure 21 and Table 11 display actual product X and product Y losses during past production peaks. It also shows the results of two simulations for each of the historical peaks. To interpret the figure and table refer to the data for peak 6 as an example. Actual product Y loss was 20.8 units and actual product X loss was 4.0 units. The results of the 36 hour schedule simulation in which process X and process Y both run with a target cycle time of 36 hours is 10.2 units of product Y lost and 0 units of product X lost. In the process X 48 hour scenario, process Y runs a 24 hour cycle and the expected product X loss is14.4 units while expected product Y loss is 0 units. Based on actual upstream production levels and peak duration the simulation shows how much of product X or product Y would have been lost under each of the two potential scheduling options. In either scheduling scenario the leading process has 0 units of loss expected.

The next section interprets the results of this simulation and the implications for managing the process X and process Y system.

3.4 Discussion

Shared resource conflicts contribute to the overall system variability for process X and process Y. This variability is one contributing factor to a trend of recent poor performance in the system. One logical method for improving system performance is to remove the shared resource constraints eliminating a source of variability and thereby improving the system. Unfortunately removing the resource constraints is not a short term possibility. This leaves us the task of minimizing the impact to the system. The previous section presented a method for calculating the impact of two scheduling options as potential solutions. The data shows us three things. First, production peaks with low total utilization do not benefit from either scheduling scenario. Second, the scheduling options represent a significant improvement opportunity over the current state for peaks with high utilization. Third, scheduling alone does not allow the system to achieve optimum performance as measured by product loss or optimum cycle time.

Recall Figure 9 which shows process X upstream utilization. The utilization trend did not increase sharply until after Year 2. Peak 3 occurred in Year 2 resulting in a total of 6.8 units of product Y lost and 0 units of product X lost. In either proposed scheduling scenario the losses are worse. The 36 hour schedule scenario predicts losses of 28.3 units of product Y lost while the 48 hour scenario predicts losses of 30.9 units of product X lost. This demonstrates that when utilization is low and available time on shared resources is plentiful dealing with resource conflicts on an as needed basis is preferable to a fixed schedule with a certain amount of expected loss every cycle.

Production peaks 4, 5, and 6 occurred during periods of higher product X upstream utilization. As we see in the data this led to higher product losses. In these scenarios the 36 hour fixed schedule options seem to offer a significant benefit. It also appears that as managers and system schedulers reacted to

resource conflicts for each of these peaks they prioritized product X over product Y. The product Y losses are significantly higher for each peak both in absolute terms and in percentage of total throughput for each product (data not available due to confidentiality). The 36 hour schedule represents a 31% improvement over actual product Y lost in peak 4, a 43% improvement in peak 5, and a 51% improvement in peak 6. These improvements are in addition to the target product X losses of 0 units for each peak under a 36 hour schedule.

The 48 hour schedule scenarios result in higher product X losses for each peak except for peak 5 which shows a 10% product loss reduction. For peak 4, product X losses increase 276% over actual and for peak 6 they increase 260%. This is a steep price to pay for the benefit of 0 product Y losses in each peak. The relative performance of product X losses versus a fixed schedule supports the theory that, implicitly or explicitly, historical ad hoc scheduling decisions were made to prioritize product X output.

The simulations conducted to compare actual past process X and process Y performance to theoretical performance of fixed, resource dependent schedules shows the potential for lower product losses. It also reveals that a target of zero product losses is not achievable under the current utilization levels with existing variability. Scheduling changes should help eliminate some variability from the processes, but additional effort, resources, and tools are required to achieve maximum performance.

It is important to note that the performance of the process X and process Y system in any of these scheduling scenarios is dependent on operational execution. The targeted loss in any one of these scenarios represents a theoretical bound for product loss. Achieving these goals would require meeting the defined cycle time targets for each process. These are achievable schedules based on resource availability, but perfect adherence would still result in the projected product loss. Failure to achieve cycle time targets would cause additional product loss above and beyond the losses due to scheduling.

3.5 Conclusion

The first analysis conducted as part of this research identified underlying causes of reduced system performance. Utilization of product X upstream systems increased over time putting pressure on critical resources that process X and process Y share. Process Y sub-step average cycle times also increased over time due to increased work content which also impacted resource utilization. Historical data shows that both processes already had a high level of cycle time variability. This variability combined with the utilization increase resulted in disproportionately higher cycle times and a decrease in performance. The second analysis of process X and process Y demonstrated the potential benefits of common factor scheduling that accounts for shared resources. It attacks both underlying causes of poor performance uncovered through analysis one. Variability is reduced because shared resource conflicts are eliminated ending the need to frequently adjust schedules. Utilization also decreases because either process X or process Y has an increased target cycle time if it is the follower process being paced by the leader. This means fewer cycles over time and more availability of shared resources.

Analysis two also showed that scheduling is not the complete answer. The simulations developed to evaluate various scheduling scenarios show that the shared resources conflicts cannot be eliminated through better sequencing. There is also no reason to believe that resource conflicts are the only source of variability in the system. The high levels of variability during periods of low utilization support this conclusion. Fixed scheduling is a step in the right direction but long term performance improvement requires a longer term strategy. The final section of this document describes this strategy.

In the interest of maximizing performance over the long term, the last analysis in this document is a review of relevant operations excellence techniques and how they can be applied to process X and process Y as well as other processes at Genzyme.

4 Analysis 3 – Long Term Improvement

The final step in the performance analysis and improvement strategy for process X and process Y is creating a mechanism to continually identify, prioritize, and solve problems in the system. As we saw in analysis one, increases in utilization over time caused a decline in performance. Analysis two presented the first step in restoring higher performance through structured scheduling to avoid resource conflicts, and reduce variability. While helpful, this effort alone is not sufficient. The scheduling scenarios still result in less than perfect performance given the current constraints. Future changes to the system are also likely to arise either internally or externally. Change could take the form of a labor shortage further constraining a shared resource, or a change in market demand requiring higher levels of production. The important fact is that changes affecting the system are both likely and unpredictable. Therefore, in order to maximize performance over time, a method to identify, prioritize, and solve problems as quickly as possible is necessary. In effect, the best systems are ones that recognize change and have the tools and resources to respond rapidly. The analysis in this section proposes what such a mechanism would look like for process X and process Y.

This section of the thesis addresses the installation of a framework for long term performance improvement of process X and process Y. There is a wealth of knowledge and literature on the subject of operational excellence and process improvement. While by no means an exhaustive summary of applicable literature, the background section will review common ideas that appear again and again from the body of research. The method section describes how these ideas apply to the specific case of process X and process Y at Genzyme. The data section applies some of the concepts to historical peak production data to reveal how process improvement tools and techniques would work in practice. The discussion section reviews the changes necessary to put a process improvement framework in place for future production peaks. Finally, the conclusion section summarizes this analysis and also makes a case for expanding the findings from this research to other Genzyme production processes.

4.1 Background

There are many techniques and methodologies for process improvement. Lean, Six Sigma, Total Quality Management, Theory of Constraints, and many other practices and principles are used to manage and improve processes across all industries. A number of corporations have created their own production systems which are commonly an aggregation of many processes improvement tools and practices. The most well-known such system is the Toyota Production System (TPS), but there are many others. For readers new to the concept of process improvement, *The Machine That Changed the World* (Womack, 1990) and *Lean Thinking* (Womack, 1996) provide a good starting point.

Of the many important concepts found in process improvement research, two are logical next steps for process X and process Y. First, all of the work involved with both processes should be documented and understood by all affected parties. This is necessary to ensure everyone knows what is required of them and what is supposed to happen. The second step for process X and process Y is the formation of problem solving teams empowered to recognize, prioritize, and improve the process as necessary using the scientific method. These two steps are structural imperatives to sustained process improvement. The first step ensures everyone knows what and how work is supposed to be completed. With this expected outcome it is possible to see when deviations from this expectation happen. The problem solving teams are then able to use a variety of process improvement tools to correct the deviations and adjust the underlying model for how work is done. With these building blocks in place, teams can use a variety of process improvement tools to fix identified problems. Without these building blocks tools can be applied to the wrong areas because it is not clear where the problems are, or individuals are not empowered to fix systemic problems when they are known.

4.1.1 Understand the Work

A thorough understanding of how work is done provides the baseline for improvement. With this starting point everyone who participates in a particular process can share a vision. With a shared vision it is possible to predict how changes will affect the performance or the outcome. For example if operator A

needs to communicate with operator B to determine the correct sequence to clean equipment but A does not know when B needs information, miscommunication is possible. If operator A and operator B agree that an email at 10:00 AM daily fits both of their needs they can make it part of the process and a shared expectation. This seems like a simple concept, but as processes become more complex it is critical to define a process along multiple dimensions.

In his study of the Toyota Production System Spear described some of the key principles that make TPS so effective. Toyota specifies the content, sequence, timing, and outcome of all work conducted throughout their organization. In addition, all customer-supplier connections are direct with very simple yes or no methods to send and receive requests[23]. The customer-supplier designation includes internal and external relationships. For example an operator working at assembly station four is a supplier to the operator at assembly station five and a customer for the operator at assembly station three.

4.1.2 Solve Problems in Teams

The second common practice involves solving problems in teams using the scientific method. Once everyone understands how the process is supposed to work it becomes easier to identify deviations from that expectation. At this point it is critical that identified problems are not hidden, but are solved by teams of people using controlled experiments. In this case the scientific method refers to establishing a hypothesis of the expected result of a change to the system, then changing the system, and evaluating the results. Solving problems in this way is important for two reasons. By committing to an expected outcome a team is testing their knowledge of how a system works. In this way an outcome that reinforces the hypothesis solves the problem, but just as important an outcome that disproves the hypothesis provides a learning experience for everyone on the team. Successful problem solving improves the system, but unsuccessful problem solving improves the teams' understanding of the system. In *The Machine That Changed the World,* Womack recognized that the skills required of the front line worker in a lean system were different than those of a traditional mass production worker. In particular creativity

[23] (Spear & Bowen, 1999)

and team work are critical.[24] Describing the case of an American company on a lean journey in *Lean Thinking* Womack talks about teams working together to eliminate the root cause of problems when performance trends deviate from target.[25] Spear also identifies team problem solving using the scientific method as a cornerstone of Toyota's success.[26]

Creating a common understanding of the work conducted for process X and process Y and establishing problem solving teams to address problems that arise is a logical next step for Genzyme. Making these changes will require additional analysis beyond what is presented in this thesis and some organizational flexibility. The next section presents a hypothetical framework for one step in process Y and shows how the improvement process might work.

4.2 Data

The following chart and graphics represent an example of the definition of work for step 1 of process Y. The content, sequence, timing, and outcome of each step in the process are defined and in this theoretical example are agreed upon by the individuals involved in completing the work.

[24] (Womack, The Machine That Changed the World: The Story of Lean Production, 1990)
[25] (Womack, Lean Thinking: Banish Waste and Create Wealth in Your Corporation, 1996)
[26] (Spear & Bowen, 1999)

Table 12 - Sub-Step Work Content Example

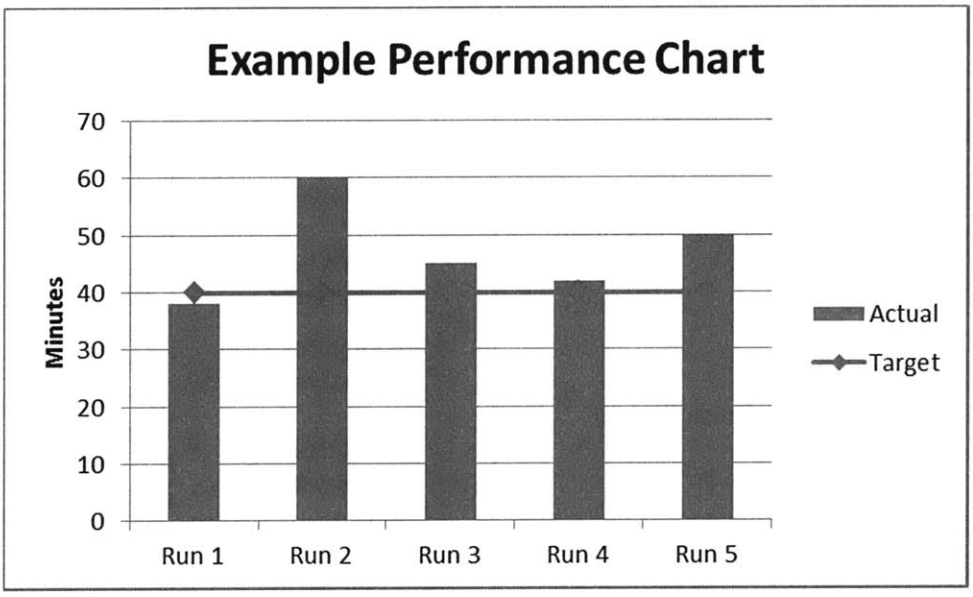
	Location: Conference Room A	**Timing: Daily 8:00AM**		
Item (Sequence)	**Task Name (Content)**	**Performed By**	**Outcome**	**Duration (Timing)**
1	Review Cleaning Paperwork	Quality Assurance Analyst Manufacturing Supervisor	Understood Verified and Approved Paperwork	15 Minutes
2	Review Batch Record	Quality Assurance Analyst Manufacturing Supervisor	Understood Verified and Approved Batch Record	20 Minutes
3	Sign Off	Quality Assurance Analyst Manufacturing Supervisor	QA Signed Batch Record Ops Signed Batch Record	5 Minutes
			Target	**40 Minutes**

This simplified example chart lets everyone associated with the work task know what is expected of them, when, and defines a successful effort based on outcome and time.

Once a model of the work is complete and agreed upon, a team working on the process will need to understand how actual performance compares to the expected outcome. A feedback mechanism such as an automated version of the data analysis completed in this project would provide system operators with the necessary data. The data historian records information in real time. This means it is possible to display both current and historical performance of each sub-step for process X and process Y. Teams

could compare data on a run by run basis, or review trends over time and compare them to focus improvement efforts. An example output for process Y step 1 is presented in Figure 22.

Figure 22 - Example Performance Chart



A team reviewing this chart would be able to determine that while all runs deviated from target Run 2 and Run 5 were off by the greatest amount. The team could review specifics of these runs to determine root causes and evaluate solutions to eliminate the problems.

This section presents a simplified example of process improvement that could work for process X and process Y. The next section describes the steps necessary to enable a full process improvement roll-out.

4.3 Discussion

The transition to an operational improvement structure for process X and process Y requires a number of changes. Genzyme, like most other biopharmaceutical organizations, is organized as a functional organization. This can make cross-functional team problem solving difficult. Currently, a large amount of process data is collected and can be used to identify cycle time performance. However,

there is no automated system to quickly and easily format the data for analysis resulting in significant and time consuming manual manipulation of the data. Finally, characterizing all of the steps of process X and process Y at the level necessary to identify problems will require the time of some of the most critical and highly utilized human resources in the production facility.

While these investments of time, money, and focus will not be trivial, the payoff can be tremendous. A system capable of continuous improvement and adaptation to a changing environment becomes a strategic advantage. And hypothetically, if these structural enablers had been in place prior to the increase in utilization for process X it would have been possible to predict and possibly minimize the impact of a high variability, high utilization scenario.

4.3.1 Enabling Process Understanding

In the author's opinion the best method for creating a deep understanding of work content in an organization that is new to the concepts of process improvement is to have an experienced process improvement individual work with teams of employees that perform each work task. This expert provides an understanding of how to document the important aspects of the work and the employees provide an understanding of the work itself. It is critical to engage the front line workers performing the tasks to ensure their buy-in early on. At later stages their ideas and involvement will provide the mechanism to improve the process faster and more sustainably then if they were not involved.

Once a baseline is established a mechanism for feedback is necessary. Without feedback the analysis of the work becomes a static depiction of a moment in time. Ongoing feedback compared to the baseline analysis communicates the overall health of the system and helps management and employees identify positive and negative trends. Feedback will also be critical to problem solving teams to analyze the outcomes of their controlled experiments. The feedback system should be designed with the input of everyone working on improving process X and process Y. It is also a good idea to keep the feedback mechanism simple, flexible, and inexpensive initially giving people a chance to use and improve it over

time before costly information technology investments. Highly visible whiteboards are effective at displaying current process information and by transposing data to spreadsheets or databases on a frequent basis it is possible to analyze trends.

4.3.2 Enabling Problem Solving Teams

Genzyme is fortunate to have a highly skilled and engaged workforce. Most employees have a college level education and are highly knowledgeable about the work they do. Establishing effective problem solving teams becomes a question of providing the time and guidance to focus the efforts of multiple individuals into a collective effort. The teams will need to be cross-functional due to the nature of the work. It doesn't make sense for operations, quality, and other functions to attempt to independently optimize a portion of a process when they have to work together to accomplish the task. Teams should be made up of the people who actually do the work. They understand the work the best and most improvements will impact them directly and require their buy-in. Involving them on the teams can only raise the quality of improvement ideas and increase the rate of change adoption. As a functionally organized company, Genzyme will have to determine the best ways to create and manage these cross-functional teams as they will span multiple managers and spheres of influence.

The teams will require representation from people experienced with process improvement tools. With a shared understanding of the work and a mechanism for feedback teams will be able to identify problems to work on. The process improvement expert on the team can guide the group to the correct tool for a particular issue. With this support teams won't waste time reinventing the wheel.

Genzyme management will also need to think about aligning incentives for problem solving teams. The teams will consist of cross-functional representation and it will be important for everyone to view success as a team as more important than success for any one individual. Incentives could take the form of a monetary team reward for achieving targets, a simple recognition award to highlight and reinforce

participation, or any number of alternatives. The desired result is a team committed to working together to be successful.

4.4 Conclusion

The analysis of process X and process Y highlights a number of important lessons for Genzyme. First, performance as measured by product loss and cycle time has declined due to an increase in utilization on an already variable process. Second, resource-based scheduling can reduce the variability associated with conflicts and reduce the total expected product loss during peak production, but is not sufficient to reach optimal performance. Finally, process improvement methodologies have proven beneficial in many applications and industries and require a fundamental framework in order for specific tools to be effective.

Process X and process Y are representative of many of the production processes at Genzyme. The analysis and recommended next steps identified in this research can be applied to many other areas. Key takeaways include the importance of understanding work at its fundamental levels as well as how processes perform over time. Performance data without an understanding of the work is hard to explain. Understanding of the work without performance data is only relevant for a short period of time. It is also important to understand the interactions between dependent processes. The issues discovered with shared resources between process X and process Y were not initially obvious until a thorough study had been conducted. Finally, empowering cross-functional work teams with support from process performance experts is a sustainable way to monitor and improve systems.

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Bibliography

Armstrong, D. (2009, June 17). Genzyme Shuts Down Plant Tainted by Virus. *The Wall Street Journal*, p. B1.

Cimiluca, D., & Whalen, J. (2010, October 5). Sanofi Makes Hostile Bid, Adding Pressure on Genzyme. *The Wall Street Journal.*

Dow Jones Business News. (2010, March 22). Icahn Reaches Deal With Biogen, Urges More Change. *Dow Jones Business News.*

Genzyme. (2010). *Genzyme Annual 2009-1.* Retrieved February 25, 2011, from Genzyme Corporation 2009 Annual Report: http://www.myvirtualpaper.com/doc/Home/genzyme-annual-2009/2010033101/#34

Genzyme Corporation. (2002-2011). *Corporate Info: Who We Are.* Retrieved February 25, 2011, from Genzyme: http://www.genzyme.com/corp/structure/corp_home.asp

Genzyme Corporation. (2009, June 25). *Genzyme News.* Retrieved February 25, 2011, from Genzyme Reports Progress Related to Allston Plant: http://www.businesswire.com/portal/site/genzyme/index.jsp?ndmViewId=news_view&ndmConfigId=1019673&newsId=20090625005653&newsLang=en

Genzyme Corporation. (2011). *Genzyme Ebook.* Retrieved February 25, 2011, from Genzyme Corporate History: http://www.genzyme.com/corp/anniversary/index.html

Genzyme Corporation. (2011, January 11). *Genzyme Financial Recovery Continues in Fourth Quarter.* Retrieved February 25, 2011, from Genzyme News: http://www.businesswire.com/portal/site/genzyme/index.jsp?ndmViewId=news_view&ndmConfigId=1019673&newsId=20110111006630&newsLang=en

Genzyme Corporation. (2011, January 21). *January 2011 Cerezyme Supply Update*. Retrieved February 25, 2011, from Genzyme Supply Update: http://supplyupdate.genzyme.com/weblog/2011/01/index.html

Gross, D., & Harris, C. M. (1998). *Fundamentals of Queueing Theory.* New York: Wiley.

Hopp, W. J., & Spearman, M. L. (2001). *Factory Physics: Foundations of Manufacturing Management.* Boston: Irwin / McGraw-Hill.

Hopp, W. J., & Spearman, M. L. (2004). To Pull or Not to Pull: What is the Question? *Manufacturing and Service Operations Management*, 133-148.

Kingman, J. (1961). The Single Server Queue in Heavy Traffic. *Proceedings of the Cambridge Philosophical Society*, 902-904.

Klassen, R. D., & Menor, L. J. (2007). The process management triangle: An empirical investigation of process trade-offs. *Journal of Operations Management*, 1015-1034.

Little, J. D. (1961). A Proof for the Queuing Formula: L= W. *Operations Research*, 383-387.

Nicholson, C. V. (2010, October 4). *Sanofi Goes Hostile With Genzyme Bid.* Retrieved February 10, 2011, from New York Times.Com: http://dealbook.nytimes.com/2010/10/04/sanofi-goes-hostile-with-genzyme-bid/

Reuters News. (2010, August 13). Key Dates in Genzyme's Manufacturing Crisis. *Reuters*.

Serafino, P. (2011, April 5). *Sanofi now holds 84.6% of Genzyme*. Retrieved April 20, 2011, from Boston.Com: http://articles.boston.com/2011-04-05/business/29385097_1_genzyme-chris-viehbacher-euros-in-paris-trading

Spear, S., & Bowen, H. (1999). Decoding the DNA of the Toyota Production System. *Harvard Business Review*, 97-106.

United States Food and Drug Administration. (2008, October 10). *fda.gov/downloads.* Retrieved February 25, 2011, from Electronic Reading Room - FDA: http://www.fda.gov/downloads/AboutFDA/CentersOffices/ORA/ORAElectronicReadingRoom/UCM175782.pdf

United States Food and Drug Administration. (2009, November 13). *fda.gov/downloads.* Retrieved February 25, 2011, from Electronic Reading Room - FDA: http://www.fda.gov/downloads/AboutFDA/CentersOffices/ORA/ORAElectronicReadingRoom/UCM191991.pdf

United States Food and Drug Administration. (2010, May 24). *FDA Press Announcements*. Retrieved February 25, 2011, from Genzyme Corp. Signs Consent Decree: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm213212.htm

Womack, J. P. (1990). *The Machine That Changed the World: The Story of Lean Production.* New York: Harper Collins.

Womack, J. P. (1996). *Lean Thinking: Banish Waste and Create Wealth in Your Corporation.* New York: Simon & Schuster.